ANNALS OF
INTERNAL MEDICINE

VOLUME 42 APRIL, 1955 NUMBER 4

AMEBIASIS: CONTROLLED LINEAR STUDIES ON NONDYSENTERIC AND MILD HEPATIC FORMS IN EGYPTIANS *

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SINCE the early part of this century many experienced observers—Osler,[1] Councilman,[2] Musgrave,[3] Craig,[4] to mention only a few—have noted the absence of a history of appreciable diarrhea or any dysentery in many cases of amebiasis which eventually prove to be severe or even fatal. Recently, Radke [5] analyzed 68 fatal cases with adequate clinical data in which amebiasis at autopsy was the primary cause of death, and pointed out that the clinical diagnosis was incorrect in 76%. Snell,[6] among others, has pointed to the preponderance of amebic lesions in the right half of the colon as the explanation of why so many patients have little or no diarrhea. The resultant clinical picture of nondysenteric amebiasis described by him and many others [4-17] in both tropical and nontropical climates during the past 15 years is, in his opinion, the very one upon which grave complications are most often superimposed. Anderson, in his recently published book "Amebiasis, Pathology, Diagnosis and Chemotherapy" [18] describes nondysenteric amebiasis first in his chapter on "Symptomatology and Clinical

* Received for publication August 19, 1954.

The opinions or assertions contained herein are the private ones of the authors and are not to be construed as official or reflecting the views of the Navy Department or the naval service at large.

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Manifestations." He gives as the reason for this the greater frequency of this form of amebiasis in the Western Hemisphere.

On the other hand, there appears to be a fairly large body of opinion, espoused chiefly by European laboratory parasitologists, and articulately expressed by Hoare [19] recently, that the two dominant forms of amebiasis are amebic dysentery and particularly the so-called "healthy carrier states." This is partly due to the belief in two distinct species or subspecies of *Endamoeba histolytica:* a pathogenic and a nonpathogenic form. Even the foremost proponents of this school of thought differ among themselves as to classification. To illustrate the confusion: Brumpt's pathogenic *E. dysenteriae* is Hoare's *E. histolytica histolytica,* whereas the school headed by Craig and Faust,[20] Sapero and Hakansson,[21] Chandler [22] and Anderson and his associates [18] simply call these the large race of *E. histolytica.* Brumpt's *E. dispar*—considered by him a distinct, always nonpathogenic species—is Hoare's "minuta" stage (12 to 13 microns, according to Elmassian, and 10–20 microns, according to Brug), which Hoare considers a frequently commensal form of his *E. histolytica histolytica.* Hoare's *E. histolytica hartmanni* (mean diameter, 7 to 8 microns) is considered by him to be a subspecies of *E. histolytica* and always commensal and nonpathogenic. The other school simply calls this the small race of *E. histolytica,* and implies that other, larger types belong to the large race. Anderson states that most authorities consider it less virulent than the large race.

Craig,[4] who had many years of both clinical and laboratory experience, and his adherents believe that *E. histolytica* is always an obligatory tissue parasite. Though he has admitted that "carriers" may have no symptoms for weeks or months, he was convinced that if infection continues, symptoms of at least mild degree will eventually develop.

It is beyond the scope of this paper to discuss the extent and types of evidence for and against the pathogenicity of the small race. Perhaps the main weakness in the clinical arguments against its pathogenicity is the assumption that the expressions "symptomless carriers" or "apparently healthy carriers," so frequently seen in the literature, signify, in fact, complete freedom from disease. Sodeman [14] has stated that minor gastrointestinal symptoms may be so mild that the patient comes to feel they are a part of himself and will not complain of them, but will notice their disappearance after treatment.

Very few controlled or precise data are available in the literature on the natural history of human amebiasis with special reference to nondysenteric and mild hepatic forms. None could be found dealing with serial clinicocoprologic studies of subjects harboring small or large race of *E. histolytica* for a considerable period without treatment. A need for further investigation along these lines was expressed by Miller and Gilani,[23] whose results from a *short-term* study of intestinal amebiasis appeared to cast doubt on the clinical significance of nondysenteric amebiasis. These results were contrary to those of other investigators.[7, 24] Such a need is

also indicated in an analysis of a questionnaire sent by Brooke and others [25] to members of the American Society of Tropical Medicine with special interest in amebiasis. It was for these reasons that the present study was conducted.

Materials and Methods

A single stool survey for intestinal parasites on approximately 100 Egyptian employees of this Unit revealed that 13 were positive for *Endamoeba histolytica*. These, together with 13 others who were negative on this one occasion, were selected in July, 1953, for this study. During the first two months of the study it was observed that an unexpected number of subjects who were initially negative had had one or more stools which were positive for *E. histolytica*. Six more initially negative subjects were therefore added to the series, making a total of 32 subjects. During the course of the first 24 weeks of observation prior to treatment eight subjects had to be dropped owing to their insufficient coöperation. This left 24 subjects, three of whom entered the study too late for analysis of their results for the pretreatment period.

All subjects were relatively healthy employees with generally good work records and without inordinate absenteeism. They were studied in the following manner for 24 weeks prior to treatment and for 24 weeks after appropriate antiamebic treatment.

An initial complete history and physical examination were done. A daily record was kept of the number and character of each stool and of symptoms referable to the gastrointestinal tract, i.e., flatulence, abdominal cramps of varying severity (not vague discomfort), anorexia and nausea. Weekly physical examinations were done, with particular attention to the abdomen. Abnormalities and tenderness of the colon were noted. The liver was always examined for both downward and upward enlargement and for tenderness by subcostal palpation and by compression and fist percussion of the lower thorax with comparison of each side.

A postero-anterior roentgenogram of the chest was taken at the time of the stool survey and at the end of the pretreatment period, at which time fluoroscopy was also done. Postero-anterior and right lateral chest roentgenograms were also taken three months after treatment.

Sigmoidoscopies were not done routinely, since it was believed that serial examinations of this kind would result in progressive lack of coöperation in the rest of the study and even more attrition.

Blood was drawn monthly for complement fixation tests for amebiasis.*

Normally passed stools were collected weekly and prepared immediately for direct microscopic examination with the Merthiolate-iodine-formalin ("MIF") stain-preservation technic of Sapero and Lawless.[26] The race of *E. histolytica*, either small or large, with the dividing line taken at 12

* Performed at the Army Medical Service Graduate School, Walter Reed Army Medical Center, Washington, D. C., through the kind coöperation of Dr. John Kent, Chief, Department of Serology.

microns for trophozoites and 9.6 microns for cysts (wet-fixed), were recorded. Densities were noted as follows after examination of an entire cover-slip preparation (10 to 15 minutes):

1 + = < 5 Parasites (cysts or trophozoites)
2 + = 5–15 Parasites (cysts or trophozoites)
3 + = 15–25 Parasites (cysts or trophozoites)
4 + = > 25 Parasites (cysts or trophozoites)

Stool specimens were also immediately cultured for bacterial enteric pathogens.

Other studies were done, whenever indicated, to detect other diseases which might influence the symptomatology or physical findings.

At no time during the 24 week pretreatment period did the two clinicians examining the subjects know which had negative and which positive stools, nor did the subjects know the results of their stool examinations. They were simply told that a search was being made for parasites that might require treatment. No dysenteric symptoms or frank hepatic complications developed during this phase of the study; hence no amebacides, antibiotics or sulfonamides were given during this period.

After the pretreatment period all subjects, including the controls, were given (1) a placebo for two weeks, (2) a course of Vioform (0.25 gm. four times daily) for 15 days, and (3) a course of carbarsone (0.25 gm. twice daily) for 10 days. In addition, those patients suspected of having even the mildest form of amebic hepatitis were given a course of chloroquine diphosphate, 0.6 gm. as base twice daily for two days, then 0.3 gm. as base once daily for 14 days.

At the end of the first half of the post-treatment period, i.e., after about three months, the examiners were compelled to learn the results of the stool examinations to make a preliminary analysis and report [27] and to retreat refractory cases. However, it is believed that this did not unduly influence the physical findings of the final three months of observation, since only occasional checks on results of stools were made thereafter. The examiners also realized that any "positive" case might at any time become negative for an indefinite period, and that any persistently "negative" case might become positive at any time.

Results

Pretreatment Period: Twenty-one subjects completed the 24 week pretreatment phase of this study. Two of these were found to have viable *Schistosoma mansoni* ova in their stools and sigmoidoscopic biopsy specimens, as well as symptoms and signs of this infection. They were therefore treated with Fuadin and eliminated from the pretreatment study.

On analysis of the results of the coprologic studies in the remaining 19 subjects it was found that they could be classified into three parasitologic groups:

1. A mixed group of 10 subjects who had *E. histolytica* trophozoites and/or cysts of both races either coexisting in the same fecal specimen or occurring separately in different specimens. The number of stools examined ranged from 16 to 24. The percentage of positive stools ranged from 16% to 100%.

2. A group of five subjects who had *E. histolytica* trophozoites and/or cysts of the small race only. The number of stools examined were for each case, respectively, 20, 23, 23, 24 and 24. In two of these the stools

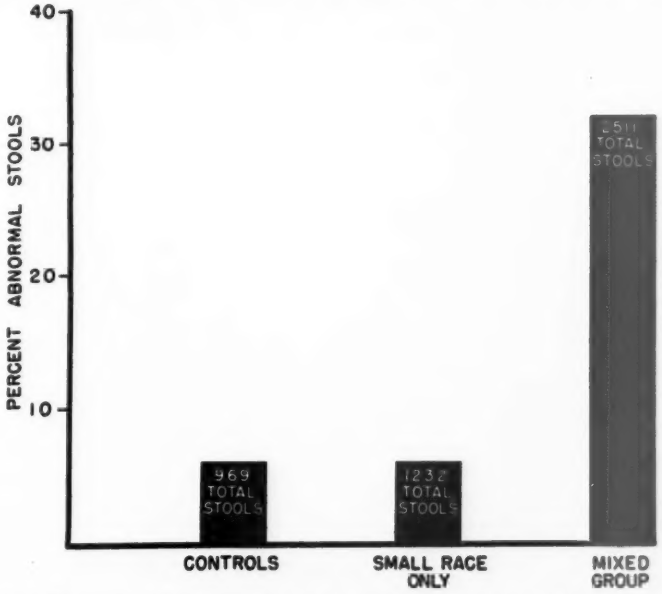

FIG. 1. Frequency of abnormal stools in 3 groups of Egyptian employees during 24 week pre-treatment period.

were positive in every examination; in the other three the percentages of positive results were 25%, 48% and 90%.

3. A control group of four subjects who had persistently negative stools in 20, 22, 23 and 24 specimens, respectively.

The total number of stools throughout the pretreatment period was determined from each subject's chart. The mean number of stools per day was calculated and found to range from 1.0 to 3.0 (mean, 1.9) for the control group, 1.0 to 2.2 (mean, 1.6) for the group with small race only, and 1.0 to 2.5 (mean, 1.6) for the group with both small and large races.

Next determined were the number of abnormal stools, which were defined to include all stools that were at least partially unformed, i.e., formed soft to mushy (commonest type of abnormal stool in each group), entirely

mushy, mushy to liquid (rare) and entirely liquid(rare). The combined total number of all stools for each group was calculated. From these figures the percentage of abnormal stools for each group was computed. The results are shown in figure 1. It can be seen that there is a fivefold difference between the percentage of abnormal stools in the control and small race groups (6% in each) on the one hand, and that in the mixed group with small and large races (32%).

Figure 2 shows the frequency of symptoms charted by patients in each group. The number of patient-days in each group represents the total number of days of observation for all the patients in that group. It is

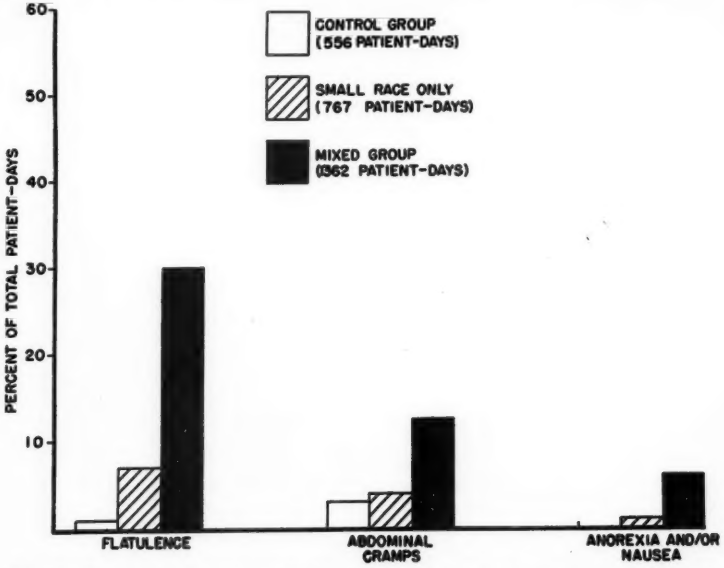

FIG. 2. Frequency of symptoms in 3 groups of Egyptian employees during 24 week pre-treatment period.

clear that the frequency of flatulence (30%) and, to a lesser extent, cramping discomfort or pain (13%) in the mixed group is considerably higher than in the control and small race groups. This is not so true for the less well defined symptoms of nausea and anorexia. The difference in frequency for flatulence between the small race group (7%) and the control group (1%) is significant.

Figure 3 shows the frequency of abdominal signs in the three groups. These are expressed as percentages of the total number of examinations, which ranged between seven and 18 and averaged 14. There is a three- to fourfold difference in the frequency of tenderness over the sigmoid in the mixed group (9%), as compared with that in the small race (3%)

and control (2%) groups. The frequency of cecal and epigastric tenderness and tenderness of a slightly enlarged liver is of an approximately similar order in the small race and mixed groups. These signs were usually sporadic and relatively mild. They were not observed in any of the examinations of the subjects with stools persistently negative for *E. histolytica.*

Post-treatment Period: Twenty-three subjects completed the studies required for the 24 week post-treatment period. Eighteen cases analyzed for the pretreatment period were included in this group. The two patients who had concomitant schistosomiasis and were treated and considered cured

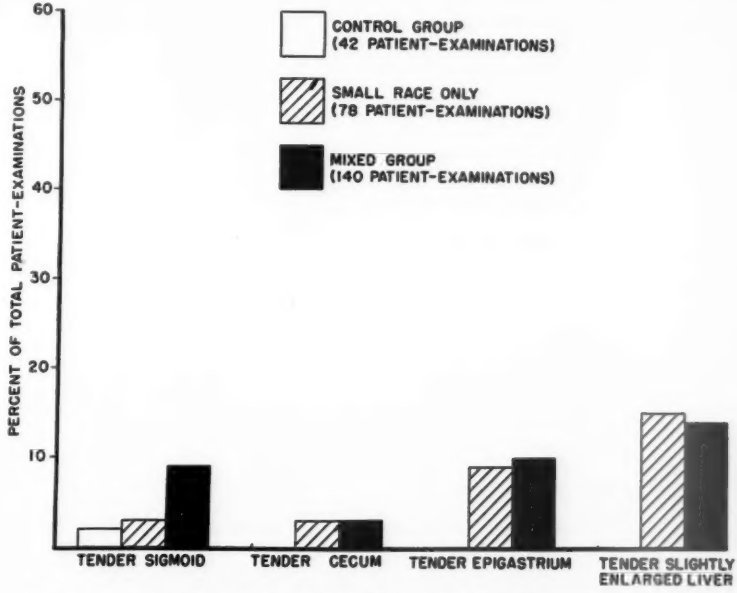

FIG. 3. Frequency of abdominal signs in 3 groups of Egyptian employees during 24 week pre-treatment period.

were also included. Three others with positive stools were included who entered the study too late for inclusion in the pretreatment series.

Analysis of the results of the coprologic studies for this period revealed:

1. A control group of 11 subjects, including the four negative controls in the pretreatment period, who remained persistently negative for *E. histolytica.* The number of stools examined ranged from 13 to 24, with the exception of one subject, who furnished only nine specimens.

2. A group of eight patients who showed *E. histolytica* trophozoites and/or cysts of the small race only. The number of stools examined ranged from 12 to 24.

3. A mixed group of four patients, three of whom revealed *E. histolytica* trophozoites and/or cysts of both races at one time or another; one patient in this group showed large race only. The number of stools examined were 13, 16, 19 and 24, respectively.

Figure 4 shows the frequency of abnormal stools in these three groups during the post-treatment period. There is a threefold difference between the control group (4%) and the mixed group (12%).

Figure 5 shows the frequency of symptoms in the three groups during the 24 week follow-up period. It is clear that the symptoms are distinctly

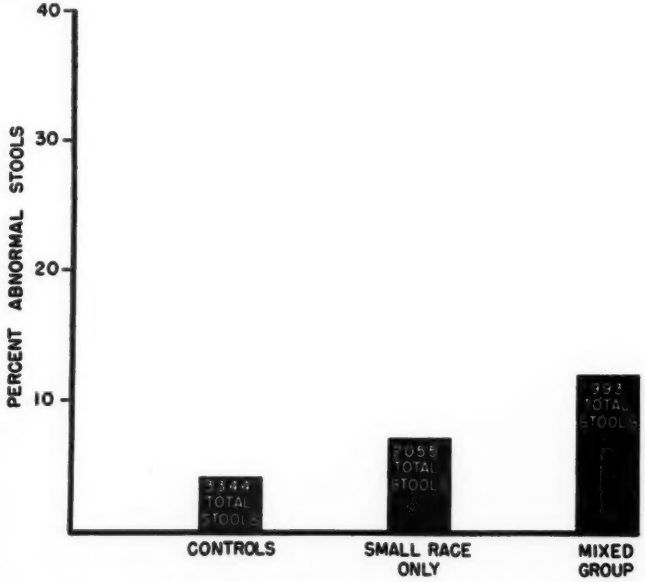

FIG. 4. Frequency of abnormal stools among 3 groups of Egyptian employees during 24 week post-treatment period.

more common in the mixed group, and to a lesser extent in the small race group, than the controls.

Figure 6 shows the frequency of abdominal signs during the post-treatment period. Here again the incidence of signs in the control group of 163 patient-examinations (11 patients) is insignificant. But the frequency of abdominal signs for both the small race group and the mixed group, which were either refractory to treatment or possibly had reinfections, was surprisingly high, especially when compared with the signs in the pretreatment group (figure 3). However, the greater frequency of post-treatment signs is consistent with the greater frequency of post-treatment symptoms (figure 5).

Comparison of Combined Pretreatment and Post-treatment Groups: Because of the small number of cases in some groups when the pretreatment and post-treatment series were considered separately, these were combined as seen in table 1. Such a combination is believed to be justifiable because (1) the three groups after treatment were characterized by the same parasitologic criteria as those before treatment, and (2) the three groups after treatment were observed the same length of time (24 weeks) as the three groups before treatment.

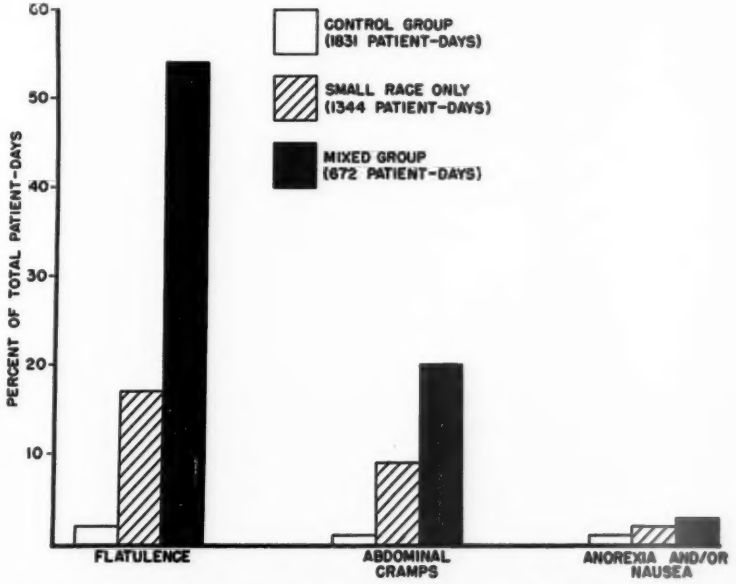

FIG. 5. Frequency of symptoms in 3 groups of Egyptian employees during 24 week post-treatment period.

The per cent of abnormal stools for the combined pretreatment and the combined post-treatment groups was calculated. A comparison of the frequencies can be seen in figure 7. The total number of patient-days for the combined groups was computed and from this was determined the percentage of days that symptoms (flatulence, cramps, anorexia, nausea) were recorded. These frequencies are also seen in figure 7. Lastly, the total numbers of patient-examinations for the combined groups were determined and from these the percentages of abdominal signs observed during the examinations computed. Figure 7 also shows these.

Comparative Observations on Seven Patients with Complete and Persistent Parasitologic Responses to Treatment: Figures 8, 9 and 10 show

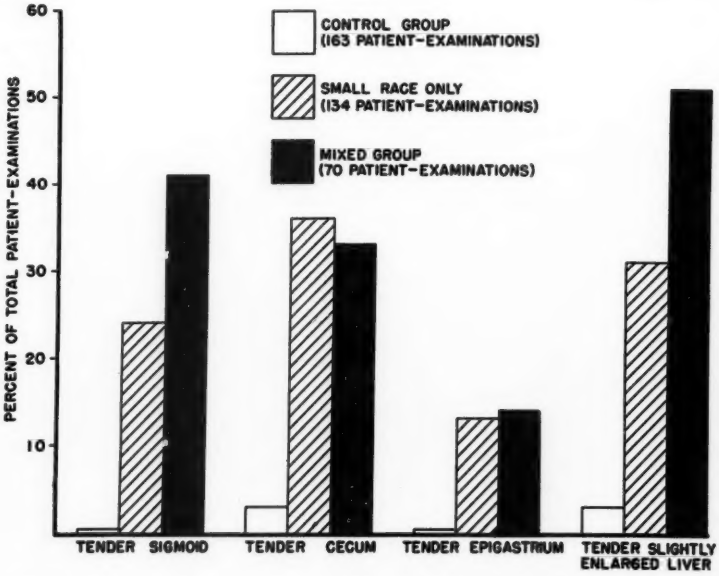

FIG. 6. Frequency of abdominal signs in 3 groups of Egyptian employees during 24 week post-treatment period.

observations on the seven patients with either or both races before treatment, and persistently negative stools for *E. histolytica* after treatment. The comparatively low frequencies of symptoms and signs before treatment might be attributed to the fact that all these cases, with the exception of one, were the mildest of the pretreatment "positive" cases. The exception was a patient with a slightly enlarged liver which was tender on seven occasions before treatment and four times after treatment. Two of the patients were persistently asymptomatic and never had any abdominal signs. One of these had both races but only a few abnormal stools (17 out of 282), and no enteric bacterial pathogens before treatment; he had no abnormal stools after treatment. The other harbored both races but recorded no abnormal stools before or after treatment. Nevertheless, he volunteered the information after treatment that his stools were generally firmer and that

TABLE 1

Number of Cases in Three Groups of Egyptian Employees before and after Treatment

	Controls	Small Race Only	Mixed Group
Before treatment	4	5	10
After treatment	11	8	4
Total cases	15	13	14

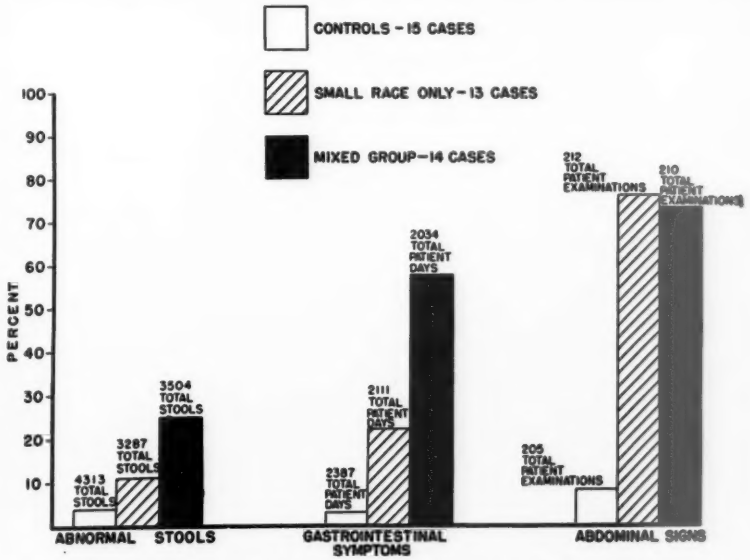

FIG. 7. Comparison of frequencies of abnormal stools, gastrointestinal symptoms and abdominal signs in combined pre-treatment and post-treatment groups of Egyptian employees.

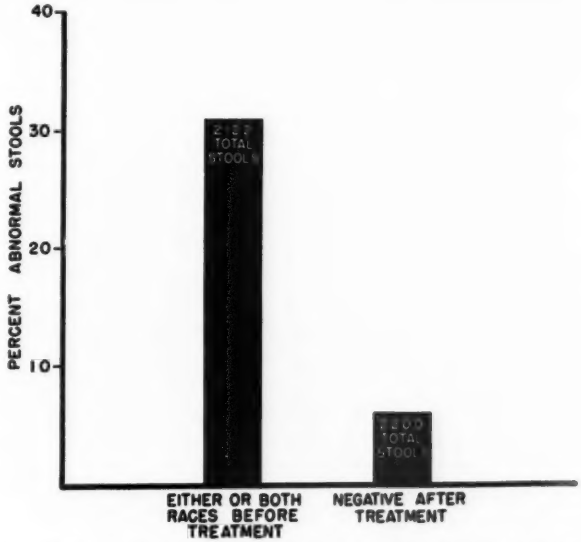

FIG. 8. Frequency of abnormal stools in 7 patients before and after anti-amebic treatment.

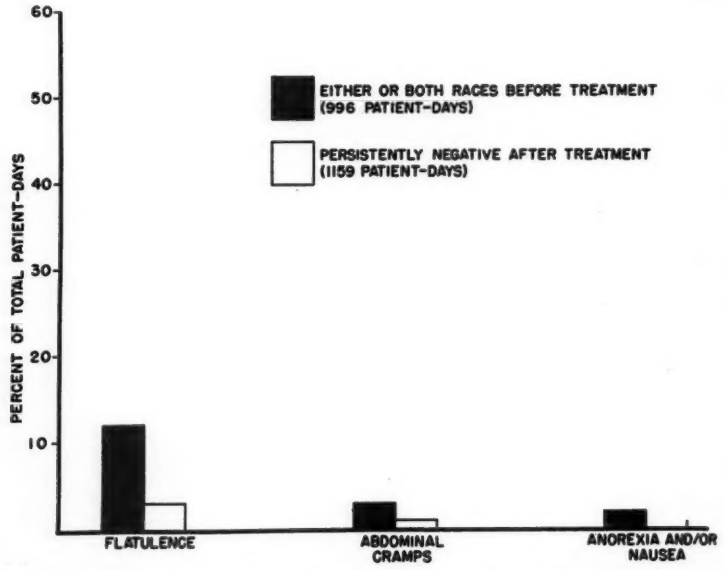

FIG. 9. Frequency of symptoms in 7 patients before and after anti-amebic treatment.

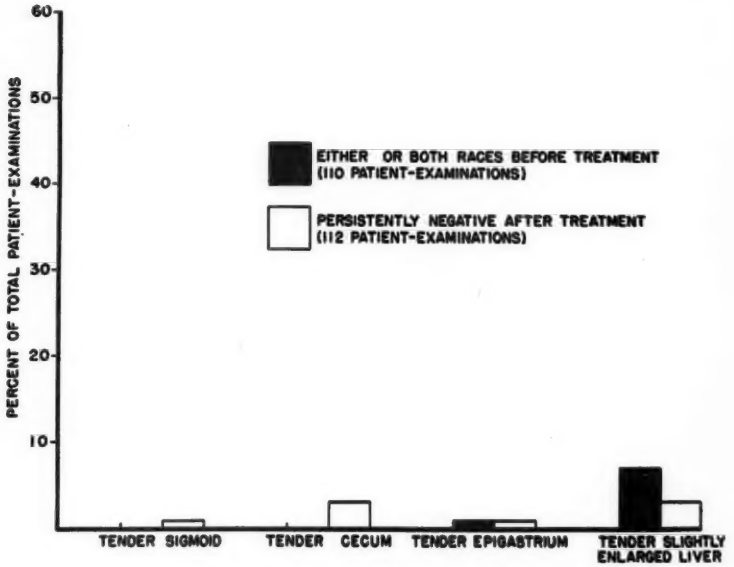

FIG. 10. Frequency of abdominal signs in 7 patients before and after treatment.

he "feels better." These two cases, as well as one with both races prior to treatment and small race after treatment, were, of all the patients, the nearest approach to the so-called "healthy carrier."

The therapeutic response of the above seven patients, who remained persistently negative after one course of Vioform and one course of carbarsone, is not to be construed as a proper measure for the efficacy of these drugs. These patients merely showed uniformly negative stools for 24 weeks after the first week treatment was started. Other patients out of the total of 23 treated showed delayed parasitologic response, or apparent initial response but subsequent appearance of positive stools. There was no way to distinguish relapse from reinfection, since all patients continued to live in the same highly endemic environment. It was therefore not the purpose of this study to evaluate the effectiveness of amebacides.

TABLE 2

Frequency of Positive Stools in Egyptians before and after Treatment

Group	Before Treatment			After Treatment		
	No. of Cases	Total Stools Examined	Per Cent of Stools Positive	No. of Cases	Total Stools Examined	Per Cent of Stools Positive
Either or both races present before and after treatment	15	324	70%	12	214	22%
Either or both races—negative after treatment	7	142	64%	7	120	0%

Influence of Frequency of Positive Stools on Parasitologic Response to Treatment: In an effort to determine whether the frequency of positive stools had any demonstrable influence on the patients' parasitologic response to treatment, these values were computed and can be seen in table 2. It would appear from these figures that the frequency with which the stools are found to be positive in such mild cases as these has no material effect on the complete response to the standard courses of treatment given.

However, even those that continued to have positive stools after treatment showed a marked reduction in frequency of positive results (70% to 22%).

Influence of Densities of E. histolytica *on Parasitologic Response to Treatment:* Table 3 compares the densities of *E. histolytica* before and after treatment in employees whose amebae were not eradicated and the seven employees whose stools remained persistently negative after treatment. The category of low densities comprised 1 plus and 2 plus densities (cysts and/or trophozoites), as defined above, and that of high densities included 3 plus and 4 plus densities.

It can be seen that the ratio of low to high densities was 5 : 1 in both these groups before treatment. In those that continued to have positive stools there was a proportionately greater reduction in low densities, resulting in a low-to-high ratio of 3 : 1.

Correlation of Frequency of Positive Stools, Densities of Cysts and Trophozoites with Clinical State: In collating the data, no correlation could be found between frequency of positive stools or *E. histolytica* densities, on the one hand, and frequency of abnormal stools, symptoms or signs on the other.

It was also noted that none of the patients passed only cysts throughout either the pretreatment or post-treatment period. That is, at least one stool in every case showed trophozoites. None showed ingested red blood cells. No over-all correlation of either form could be made with these mild clinical states.

TABLE 3

Comparative Densities of *E. Histolytica* in Egyptians before and after Treatment

Group	Before Treatment			Ratio Low:High	After Treatment			Ratio Low:High
	No. of Cases	No. of Low Densities	No. of High Densities		No. of Cases	No. of Low Densities	No. of High Densities	
Either or both races present before and after treatment	15	303	63	5:1	12	42	13	3:1
Either or both races—negative after treatment	7	124	24	5:1	7	0	0	—

Other Parasites: Occasionally ova of ascaris, hookworm, trichostrongylus and pinworms were detected by an efficient concentration modification of the MIF technic (MIFC).[28] These always occurred in light densities and did not appear to influence the clinical states. *Dientamoeba fragilis* was encountered at times in light densities. Experience at this Unit[29] with this parasite, even in persistent heavy densities, has failed to incriminate it as pathogenic.

Bacteriologic Results: During the pretreatment period five patients had stools from which enteric bacterial pathogens were cultured. Two each had *Shigella dysenteriae 2* on one occasion, but with no concomitant diarrhea or other gastrointestinal symptoms; one was a control, the other in the mixed group. The third patient had *S. flexneri 2* once, which was associated with diarrhea, and *S. flexneri 3,* which was not associated with diarrhea. This patient, however, had schistosomiasis and was not included in the pretreatment analysis. Two other patients had, respectively, *S. flexneri 3* and *S. flexneri 4,* but failed to coöperate later and were dropped from the study.

During the post-treatment period two patients, each on one occasion, yielded cultures, respectively, of *S. dysenteriae 5* and *S. flexneri 6*; neither had associated diarrhea or other gastrointestinal symptoms. A third patient showed *S. boydii 1* and *S. boydii 5*, each associated with brief bouts of diarrhea. This case was in the mixed group, but it is considered that these episodes did not contribute materially to the combined symptomatology of the group.

Paracolons were fairly common but occurred with about equal frequency in all three groups.

Results of Complement Fixation Tests: The results of the monthly complement fixation tests were all essentially negative. It should be pointed out, however, that the sera were preserved with Merthiolate, and without freezing, for periods ranging from three to six months for post-treatment specimens and from six to 11 months for pretreatment specimens. The causes of such long storage were repeated failures to find a collaborating laboratory with a reliable antigen.

Roentgenographic Studies: The height of the right hemidiaphragm in deep inspiration was compared with that of the left in postero-anterior roentgenograms of the chest in 22 patients. The difference between the two leaves ranged between 0.5 and 3.0 cm. (mean of 2.0 cm.) for 10 subjects who received chloroquine on even the slightest suspicion of a mild amebic hepatitis. The range for these values for the other 12 patients was 0 to 3.6 cm. (mean of 1.7 cm.). No essential difference was observed in any of the cases before and after treatment.

Discussion

It can be seen that the results of this study, especially when considered collectively as shown in figure 7, support the clinical findings of others [7, 24] and the opinions of many clinicians [3, 4, 6, 8, 9, 10, 11, 13, 14, 15] based on vast experience with this disease. It is believed that only such a linear study as this can uncover mild nondysenterie cases which otherwise would be labeled as "symptomless carriers" or "apparently healthy carriers." None of the employees in this study had sought treatment for "diarrhea" or "dysentery," as indicated by their medical records during the previous year. It is doubtful that even a careful history taken at any given time during the observation period would have elicited the increased frequency of mildly abnormal stools as indicated by a daily chart in most of the cases. In this connection, it was surprising how seldom the often described bouts of constipation were reflected in the charts. If constipation is measured by the absence of bowel evacuation on one or more days, rather than an unmeasurable increased firmness of stools, this was evident in bouts in only one case, one of the severer but nondysenteric cases. Although the employees were told to record symptoms other than those analyzed (e.g., easy fatigability, vague abdominal pains, joint pains, etc.), these were not very common and were

difficult to appraise. It is obvious that the present data could not be used to determine whether they are commoner in cases with frequent constipation. Van Steenis [30] suggests that such symptoms arise from cecal stasis in cases in which the cecal pathology can be inferred to be more advanced than in the present series. In this connection, it is interesting that Mackie [31] has noted that amebiasis is frequently misdiagnosed as psychoneurosis.

The gastrointestinal symptoms of flatulence, cramping abdominal pain, anorexia and nausea, which were usually mild and recurrent, would also be difficult in most instances to elicit in the conventional history-taking.

Moreover, frequent periodic abdominal examinations with or without concomitant minor complaints recorded in the daily chart were required to bring minor intermittent signs to light.

These experiences are certainly more in accord with Craig's belief [32] as early as 1932 that 40 to 50% of "carriers" have symptoms. Craig later wrote [33] his conviction that although "carriers" (he deplores the term) may be asymptomatic for weeks or months, symptoms will eventually develop if the infection continues.

On the contrary, according to Mackie et al.,[34] some authorities believe not more than 10% of "cyst-passers" suffer damage from the infection. Elsdon-Dew [35] has stated lately that only in a small percentage of infections is there any evidence that complaints attributed to amebiasis are actually due to *E. histolytica.* In fact, he claims that amebic dysentery and liver abscess are the only indisputable examples of clinical amebiasis.

The authors agree with Craig, Anderson and many others that such a view might be hazardous when considering the indications for early treatment of so-called carriers or cyst-passers.

More objective evidence for the pathogenicity of "carrier" strains of *E. histolytica* is afforded by several human autopsy studies. As early as 1910 Musgrave [3] found varying sizes of amebic intestinal lesions in 50 cases with no history of diarrhea or dysentery. In 1925 James and Deeks found extensive amebic involvement of the colon in patients who died without a history of dysentery.[36] The most convincing findings were those of Faust,[37] who studied a series of 202 autopsies on *accident* cases and found 13 infections (6.44%) of *E. histolytica.* In five of these, and possibly two more, there was concrete evidence of tissue invasion. In three of the five cases only small race cysts (7 to 8 μ) and their trophozoites were found in the same close relation to the variable lesions (in centers or necks of lesions) as the large race trophozoites in the other two cases. Faust concluded that in these few cases—presumably without histories of significant gastrointestinal symptoms—there was no relationship between racial size of the amebae and their ability to invade the intestinal wall. It would appear that the pathology in these cases might well be similar to that postulated to account for the low-grade nondysenteric symptoms in the Egyptian employees with *E. histolytica* in the present study.

Although different races had been previously described, it was not until 1942 that two significantly distinct races were more generally accepted after the report of Sapero and his associates.[21] They noted mild complaints were not uncommon in 179 cases with small race only, but considered it exceedingly difficult to be certain that the small race was responsible. In a few cases carbarsone gave relief. However, linear studies before or after treatment do not appear to have been done.

Morton and his collaborators[38] examined three consecutive stool specimens from 1,000 adolescent males. Sixteen harbored *E. histolytica,* of which eight were large race and seven small race. None of the 16 boys appeared to have suffered from symptoms referable to the infection. Here again, apparently no serial clinical studies were done.

From a study of 164 patients with gastrointestinal disorders, of whom 21 harbored *E. histolytica* of the small race trophozoites only, Sonntag[39] concluded that this parasite is always pathogenic.

Frye and Meleney[40] cultivated a small race strain through many subcultures for eight months. The cysts and amebae retained their small size. Five out of 22 kittens inoculated became infected and showed superficial colon lesions. These authors also noted that the case from which this small race strain was obtained gave a positive complement fixation test which became negative after specific treatment.

Halawani et al.[41] found among 400 Egyptians a 72% incidence of "small cyst producing races." They stated that frank amebic dysentery is not common in Egypt, but did not express an opinion as to the pathogenicity of the small race in nondysenteric cases.

In any event, Anderson[18] sums up the current prevailing opinion by stating that most authorities consider the small race to be pathogenic but to a lesser extent than the large race.

The question of how often the so-called "cyst-passer" also passes trophozoites is fraught with a wide divergence of opinions. In general, one can infer from the pertinent literature that most who use the term imply that such individuals do not commonly pass the vegetative form. Broughton and his associates[11] made careful stool studies in 676 cases of amebiasis, chiefly mild. They concluded that the so-called cyst-passer, who was difficult to distinguish from a case of intestinal amebiasis, passes all forms, though often at different times. This view is fully in accord with the serial findings in the stools of the Egyptian employees of the present study, all of whom showed trophozoites at least once and usually oftener.

The wide variations observed in the frequency of positive results and densities of infection and the apparent lack of their correlation with symptoms or signs were interesting. This is especially true in view of the fact that most, if not all, symptoms and signs were minimal or close to minimal.

The parasitologic findings in the present study in general appear to be similar to those of Marsden.[42] Among other similarities, several of the Egyptian employees during the pretreatment period remained "negative"

for a long interval, one as long as 12 weeks. Whether this was a spontaneous complete remission followed by a reinfection, or a spontaneous reduction in density to levels impossible to detect even with 11 weekly examinations, is impossible to determine. Spontaneous complete remissions have been presumed by Craig,[4] Jones [43] and Frye and his co-workers.[44] As the latter point out, such remissions must be borne in mind in evaluating the efficacy of any form of treatment.

In figures 5 and 6 it can be seen that the symptoms and signs during the post-treatment period were substantially more frequent than those in the pretreatment period (figures 2 and 3). At least a partial explanation is that the milder cases of the pretreatment group were cured by therapy and thereby transferred to the control group. This left only those with more marked signs and symptoms among those still positive for amebae in the post-treatment series.

Since Rogers [45] first emphasized both the clinical and the pathologic distinction between amebic hepatitis and abscess there has been a growing recognition [46–52] of the common occurrence of the earlier forms of liver involvement. Clark [46] as early as 1925 found in Panama that about 50% of autopsies on 186 amebics revealed some degree of liver involvement. Payne [49] in 1945 reported clinical diagnoses of mild amebic hepatitis in 50% of 1,000 cases of amebiasis in India. Banker [52] reported on 66 cases of hepatic amebiasis, diagnosed at autopsy; even though all these had one or more abscesses, only about 40% had given a history of dysentery, and concurrent amebic ulcers in the colon were not found in nearly 25%. The ulcers that were found were more common in the proximal colon.

There is uniform agreement among all experienced with amebic hepatitis that tenderness and enlargement are the most important and constant signs. A history of diarrhea or dysentery and detection of *E. histolytica* in the stools are of course helpful in leading to suspicion of this complication, particularly in a nonendemic area. But Snell [6] has stated that, for every diagnosis made by finding amebae in the stool, one is made by therapeutic trial with emetine. The complement fixation test with a reliable antigen appears to be of great aid in most cases, especially with reversal in antibody titer after emetine or chloroquine treatment. Roentgenographic and fluoroscopic study for abnormal elevation, tenting and fixation is useful in cases with significant involvement of the upper portion of the liver.

Sodeman and Lewis [48] reported a series of 33 cases of amebic hepatitis, all of whom had findings of active hepatic disease. Five of these had clinical jaundice. All but eight had a dramatic onset. Even the eight chronic cases, however, did not have the low-grade symptomatology described by Hurst [53] and Castellani.[54] These authors are referred to by Sodeman as describing an ill-defined picture of minimal aching and tenderness over the liver, with or without slight downward enlargement, associated with anorexia and easy fatigability but in the absence of fever or leukocytosis. Sodeman admitted that such clinical states are possible but not proved. In

a subsequent report,[14] however, he states that he has seen many patients with colonic amebiasis who have slight enlargement and tenderness of the liver without chills or fever, but in whom the mild tenderness and enlargement of the liver disappear after treatment.

Sandler [55] reported a series of 47 cases of amebic hepatitis in which many features of the acute phase, such as fever, severe pains and enlargement of the liver, were absent or minimal. The chief sign was liver tenderness. X-rays were usually negative. No shift to the left in the leukocytes was found, even when leukocytosis was present. The blood sedimentation rate tended to become normal with increasing chronicity. A complement fixation test, however, was positive in 20 of the 25 cases in which it was performed. Emetine had no conspicuous effect in this chronic form of amebic hepatitis.

Lane [56] reported 20 cases of hepatic amebiasis, all with moderate or severe liver tenderness, which he treated with chloroquine. The more chronic cases accompanied by clinical gut involvement showed variable responses.

As stated above, it was not the purpose of the present study to test the efficacy of any drug. The 10 cases in which low-grade hepatic involvement was considered possible were given one course of chloroquine at the end of the pretreatment period. The preliminary analysis of the data did not indicate significant improvement in the group as a whole. Improvement in such low-grade chronic cases chiefly with intermittent pretreatment liver tenderness would be difficult to detect, particularly if response is delayed or partial. A second course of chloroquine was given to four patients, but follow-up has been too short for evaluation.

Possible explanations for the essentially negative results of the complement fixation tests are: (1) loss of antibodies in the sera due to prolonged storage without freezing; (2) insufficient tissue invasion in these mild cases to evoke detectable pretreatment antibody levels; (3) causes other than *E. histolytica* producing the observed intermittent tenderness of slightly enlarged livers.

The results of the comparative roentgenographic studies, though showing a slightly higher mean value for the level of the right diaphragm in the group suspected of having mild hepatic involvement, cannot be interpreted as significant. This is not surprising in view of the low-grade nature of the physical signs.

It should be noted, however, that every case suspected of having liver involvement during the "double blind" pretreatment period, with one exception, continued to show *E. histolytica* in the stools during the post-treatment period. The exception, on the other hand, showed distinct improvement during the first half of the post-treatment period (which was also "double blind"), and complete disappearance of signs during the remainder of the post-treatment period.

Summary

1. Serial clinicocoprologic studies were made, in a "double blind" manner, on 19 "apparently healthy" Egyptian employees during a 24 week pretreatment period.

2. Ten of these subjects showed markedly varying frequencies and densities of large and small races of *E. histolytica* (mixed group). This was also true for five subjects who revealed small race amebae only in their stools. Four subjects had persistently negative stools.

3. The mixed group had a distinctly higher frequency (32%) of abnormal stools than the small race group (6%) and control group (6%). The mixed group also had a higher frequency of flatulence (30%) and abdominal cramps (13%) than the small race group (7%, 4%) and control group (1%, 3%).

4. Abdominal signs, including intermittent mild tenderness of a slightly enlarged liver, were rather frequently observed in the mixed and small race groups, but were virtually absent in the control group.

5. Serial clinicocoprologic studies were also made on 23 Egyptian employees, including 18 of those in the pretreatment series, during a 24 week post-treatment period.

6. In the post-treatment series, 11 subjects remained persistently negative, eight showed small race only, and four were assigned to a mixed group.

7. The post-treatment mixed group and, to a lesser extent, the small race group showed higher frequencies of abnormal stools, flatulence and abdominal cramps than the control group. Here again, abdominal signs were only rarely observed in the control group as compared with the mixed and small race groups.

8. Combining the three similar groups in the series before and after treatment gave a total of 15 controls, 13 small race cases and 14 mixed cases. Computation of frequency of abnormal stools and gastrointestinal symptoms again showed definite preponderance for the mixed group and, to a lesser extent, for the small race group, over the control group. Abdominal signs were about seven times as frequent in the mixed and small race groups as in the control group.

9. Comparison of seven milder cases which had either or both races before treatment and were persistently negative after treatment showed reversal, in general, of symptoms and signs to control levels.

10. The findings of the present study are interpreted as clinical support for the concept of mild pathogenicity of the small race and for the concept that "apparently healthy carriers" of either race may have mild symptoms and signs of amebiasis if followed serially over a long enough period.

Addendum

A preliminary report received on the results of the complement fixation tests was "essentially negative" as stated above under *Results of Comple-*

ment Fixation Tests. Further analysis of these results showed the following: Four of the 10 cases suspected clinically of having chronic low-grade amebic hepatitis revealed one or more positive reactions (weak or strong) to the complement fixation test and reversal to negative after chloroquine treatment. Three of the cases not suspected clinically of having hepatic involvement, and hence not treated with chloroquine, had one or more positive reactions. All of these cases except one of the latter three had stools positive for *E. histolytica.*

ACKNOWLEDGMENTS

The authors are grateful to Dr. M. M. Brooke, Chief, Parasitology and Mycology Section, Communicable Disease Center, Chamblee, Georgia, for his kind assistance in obtaining the generous services of Dr. John F. Kent, Chief, Department of Serology, Army Medical Service Graduate School, Walter Reed Medical Center, Washington, D. C. Grateful acknowledgment is made to Captain A. R. Higgins, MC, U. S. Navy, former Director of NAMRU-3, and to Dr. John H. Killough for reviewing the manuscript and for their valuable suggestions.

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CLASSIFICATION OF ALLERGIC REACTIONS *

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INTRODUCTION

CLINICAL allergic reactions are not all dependent on the same immunologic mechanism. It is the purpose of this review to assemble all the varieties of allergic reactions and divide them into groups according to their basic immune mechanisms. With this knowledge it might be expected that it would be possible for the attending physician to classify any given allergic clinical reaction.

Correct classification of a given allergic reaction according to immunogenesis is highly desirable, since successful management can be more readily achieved if the various attributes of the different classes are appreciated. Not only may medication which would be helpful for the members of one group be valueless, or at times even harmful for the members of another group, but also the ultimate purpose—detection of the antigen—is achieved more readily.

The situation is somewhat analogous to that which exists in any branch of internal medicine. The attending physician may, for example, treat congestive heart failure without knowledge of the correct classification of the underlying heart disease. But he can never successfully manage the patient without knowledge of the factors operating in this patient's heart to produce congestive failure.

Specialized hematologic aids are not available at the bedside. Although this classification is based on information derived from hematologic investigation, nevertheless there are clinical features peculiar to each group and subgroup, and it is to be hoped that an awareness of these clinical differences would enable one to arrive at a correct classification diagnosis. The two most outstanding features are, first, the general characteristics of the clinical reaction, and, second, the time interval between challenge and development of the reaction. It is advantageous in reading the accompanying tables to remember these two basic features.

The first of these, the characteristics of the clinical reaction, embraces such things as the duration of the reaction; the degree and type of constitutional participation, which includes the presence or absence of fever and the presence or absence of infection; the presence or absence of shock; and, whenever visible, the gross appearance of the lesion. In short, the attending physician at the bedside should attempt to visualize as thoroughly as possible the pathology or the disturbed physiology.

* Received for publication June 7, 1954.

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The second important feature, the time interval between challenge and development of reaction, implies knowledge, or at least suspicion of the nature of the antigen. Since identification of the antigen is the ultimate goal in allergic disease management, it would perhaps appear paradoxic that the physician should, at his initial approach to the patient, formulate an opinion about the nature of the antigen. But it is surprising how often it is in fact possible to formulate such an opinion initially. It is true that this formulation can usually be deduced from history only in those reactions that are isolated and episodic in occurrence. However, even in chronic reactions due to close spacing of repeated exposures, or to prolonged retention of the antigen, or to continuous propagation of the antigen within the host, it is at times possible by careful bedside survey to formulate an opinion about the nature of the antigen involved. When it is possible to do so, measurement of this important time interval helps greatly in immunogenetic classification.

A. Objective evidence

I. Plasma antibody

a. Formation — Table 1
b. Immediate reactions — Table 2
(1) Role of histamine — Table 3
c. Reactions developing hours later — Table 4

II. Lymphocyte antibody

a. Formation — Table 5
b. Reactions — Table 6

III. Plasma and lymphocyte antibody

a. Formation — Table 7
b. Reactions — Table 8

IV. Fixed vascular reactions developing days later — Table 9

B. Clinical correlation

Plasma Antibody Formation (Table 1)

This develops naturally in a small percentage of the population (A), and artificially in most of the population if satisfactory conditions are met at the time of preparation (B). Preparation is usually in the form of spontaneous disease (C), or by injection of a variety of antigens (D), which are usually water-soluble. Some antigens may give rise to the development of plasma antibody when the route of artificial contact is other than injection. In general, naturally developing plasma antibody is usually reagin, whereas artificially developing antibody is more likely to be precipitin (E). There are exceptions to this rule.

Serum from an animal or patient with plasma antibody, when given to a normal animal of the same species, will generally passively sensitize the recipient (F).

TABLE 1

Plasma Antibody Formation

	Animal	Preparation	Antibody			
			Reagin	Non-Precipitating Antitoxin	Precipitating Antitoxin	Precipitin
A	Man 5	Naturally exposed	Small percentage			
B	Man 6, 7, 8	Artificially exposed large quantity serum, Ascaris, Trichina	Large percentage			
C	Man 1, 2, 3, 4	Hay fever	+			
C	Man 1, 2, 3, 4	Certain spontaneous diseases	+			
C	Man 1, 2, 3, 4	Spontaneous epidermal diseases	Large percentage			
D	Man 1, 2, 3, 4	Single "booster" diphtheria toxoid	40%			
D	Schick neg. man 1, 2, 3, 4	Single "booster" diphtheria toxoid		50%	100%	
D	1, 2, 3, 4	Encapsul. pneumo. I. V.	+			
D	1, 2, 3, 4	Bacter. polysaccharides	+			+
D	1, 2, 3, 4	Soluble, readily absorbable antigens	+			+

	Animal	Preparation	Antibody		
			Reagin	Thermostabile	Precipitin
E	1, 2, 3, 4	Bacter. cells extracts			+
E	1, 2, 3, 4	Solution bact. nucleoproteins			+
E	Man 9	Hay fever treated specific antigen	+	+	
E	Man 10	Diabetes, insulin sensitivity and fastness	+	+	
E	Man 11	Serum sickness			+
E	Man 1, 2, 3, 4	Serum reactions	+		+
F	Man 12, 13	Reagin serum skin (latent required)	Challenge antigen skin or antigen ingest.		Positive local
F	G. pig 1, 2, 3, 4	Antibody passively	Challenge antigen circulation		Anaphylaxis
G	Rabbit 14, 15	Antibody forming disease treated ACTH, cortisone	Cessation antibody production		

Cortisone treatment eventually results in cessation of plasma antibody production (G). However, if conditions are such that the host is continuously exposed to the antigen, plasma antibody formation will be resumed shortly after cessation of cortisone therapy.

Plasma Antibody Reactions, Immediate (Table 2)

In the normal animal the introduction of antigen results in perivascular neutrophilic infiltration (H), most pronounced around the small vessels that directly transport the material downstream, persisting for about 48 hours. In the plasma-antibody sensitized experimental animal or patient, re-introduction of the antigen produces explosive dynamic vascular reactions, occurring within 15 minutes (I). The components of these vascular reactions disappear within one hour, except perhaps for the agglutinated masses of platelets and leukocytes.

It can hardly be doubted that the phenomena seen here are the direct result of union of antigen with antibody in the plasma. When the union has been effected completely, as it so quickly must be (J), the stimulus is no longer present and the allergic reaction stops.

In some instances the mere presence of both antigen and antibody in the plasma results in no reaction, but when a different antigen is added to the plasma the initially expected reaction develops. This is classically seen in allergic thrombocytopenic purpura, in which an anti-platelet antibody can usually be found in the plasma, but in which disease, ingestion of a particular food or drug (K) is required to produce purpura and thrombocytopenia. Even in the absence of a clinical reaction the patient's blood will, when transfused into a normal individual, cause purpura and thrombocytopenia. There is no available explanation for this requirement of an additional antigen.

Although serum from a human being with naturally occurring plasma antibody will rarely passively sensitize a guinea pig (L), serum from patients with serum sickness, some forms of severe asthma, and from a guinea pig rendered antianaphylactic due to sensitization with an excessive amount of antigen will passively sensitize a normal guinea pig (M), so that, after a short incubation period, systemic challenge will produce anaphylactic shock.

The state of allergy produced in man by administration of a potent antigen hypodermically may or may not be accompanied by classic reagin test reactions. These individuals may not exhibit positive skin or conjunctival test reactions (N), even though they can be thrown into immediate shock after subcutaneous or intravenous administration of the subsequent dose. However, it is also true that clinical allergy of this type to a wide variety of antigens may occasionally exist in the absence of positive skin or conjunctival test reactions (O). The reverse state, in which positive skin test reactions may exist in the absence of clinical disease on natural exposure to the antigen, may occasionally be seen.

TABLE 2

Plasma Antibody Reactions, Immediate

	Animal	Preparation	Challenge	Reaction
H	Rabbit 16	Horse serum		Normergic vascular cellular, 24–70 hours
I	1, 2, 3, 4	Sensitized	Antigen skin	Local anaphylaxis: 1) Capillary dilatation 2) Arteriolar constriction 3) Arteriolar dilatation 4) Rapid subsidence 5) Leukocytes, platelets to endothelium
	Man 1, 2, 3, 4	Natural sensitiz., reagin type	Antigen systemically	Shock
	G. pig 1, 2, 3, 4	Antiserum, small amount (latent period required)	Antigen circulation	Anaphylactic shock: 1) Complement depressed 2) Vascular phenomena 3) W.B.C. stick endothel. 4) Edema 5) Heparin increased
J	Rabbit 1, 2, 3, 4	Passive antibody	Antigen skin	¼ hour: maximal union of antigen + plasma antibody
K	Man 17	Thrombocytopenic purpura	Food or drug	1) Fall in number platelets 2) Hemorrhage
	Man 18	Serum from man with thromb. purpura		
	Species A 19	Serum from species B with thromb. purpura		
L	G. pig 1, 2, 3, 4	Human reagin serum	Antigen	None
	G. pig uterus 1, 2, 3, 4	Human reagin serum	Antigen to bath	None
M	G. pig 1, 2, 3, 4	Some human asthma, some human serum sick., 3 week serum after excess antigen	Latent required. Antigen circulation	Anaphylactic shock
	G. pig 1, 2, 3, 4	Great excess antigen. Wait 2 to 3 weeks	Antigen circul.	None
			Antigen + uterus bath	Contraction
	G. pig 1, 2, 3, 4	Great excess antigen. Wait 5 weeks	Antigen circul.	Anaphylactic shock
	G. pig uterus 11, 20	Bath, incubate with serum (some asthma, some serum sick.)	Antigen bath	Contraction

TABLE 2—*Continued*

	Animal	Preparation	Challenge	Reaction
N	Man 1, 2, 3, 4	Horse serum, penicillin, diph. toxoid, pertussis vac.	Subcutaneous	Shock
			Skin test	Positive or negative
			Conjunct. test	Positive or negative
O	Man 1, 2, 3, 4	Natural immediate type sensitization	Skin test	Usually positive
			Conjunct. test	Usually positive
P	1, 2, 3, 4	Hapten + azo dye	Hapten + azo dye	Shock
	1, 2, 3, 4	Hapten + protein A	Hapten + protein B	Shock
	1, 2, 3, 4	1) Hapten + prot. 2) Hapten repeatedly	Hapten + protein	None
Q	Man 1, 2, 3, 4	Natural or artificial sensitization	Antigen skin	Rapid reaction suggests antibody fixed locally??
	G. pig uterus 21, 22	Small amount antiserum bath. 5 hr. incubat. needed	Antigen bath	Contraction (antibody sessile??)
R	G. pig uterus 23	40 times as much antiserum bath. No incubation needed	Antigen bath	Contraction (antibody not sessile)
	Rabbit 23	Passively sensitize large amount serum. No latent needed	Antigen skin	Positive Arthus (antibody not sessile)
	Man 1, 2, 3, 4		Reagin serum + antigen	Submaximal (antibody not sessile)
S	Rabbit 1, 2, 3, 4	Antibody skin	Antigen distant skin	Arthus
T	Rabbit 24, 25	Actively sensitized, large amount plasma antibody		
		Cells. Tissue culture	Antigen	None
		Avascular cornea	Antigen	None
		Heparin treated	Antigen circ.	None
U	Rabbit 1, 2, 3, 4	Actively sensitize hemolytic antigen, then treat cortisone	Antigen circ.	Hemolytic reaction
	G. pig 1, 2, 3, 4	Actively sensitize, then treat cortisone or ACTH	Antigen circ.	Anaphylac. shock

Haptens are capable of sensitizing when mixed with an appropriate azo dye or a protein. They are then capable of shocking when administered again mixed with the same dye, or the same or a different protein, and they are capable of desensitizing when administered alone (P).

The 15 minute vascular reaction may be produced generally or locally, depending on whether challenge is general or local. The rapidity of occurrence after challenge of the local reaction (Q), as well as the necessary latent period between sensitization and challenge, was at first thought to indicate the development and presence of fixed tissue antibody. This, however, is disproved by the immediate occurrence of the reaction when the normal animal is injected locally with a mixture of antibody and antigen (R). Moreover, local sensitization will, after a time, result in generalized sensitization, as evidenced by the positive reaction to challenge of a distant skin area after local passive sensitization (S).

It appears certain that immediate types of reactions are due solely to plasma antibody and not to fixed tissue antibody, for cells from such a sensitized animal are not damaged in tissue culture when the antigen is added (T).

Corticotropin and cortisone do not interfere with antigen-antibody union in the circulation (U), or with the experimental or clinical reactions that result from this union.

Role of Histamine (Table 3)

If histamine plays a role in allergic reactions, it is active at the time of union of antigen with plasma antibody (V). Its importance would therefore appear to be limited to those reactions which take place immediately after introduction of antigen in an experimental animal or patient in whom appropriate plasma antibody is present.

A variety of substances, including histamine, are capable of producing shock indistinguishable from anaphylactic shock in the normal animal (W). This does not mean that histamine must be the mediator of immediate allergic reactions. If the uterus from a sensitized animal is repeatedly exposed to histamine in a bath, eventually the uterus will no longer contract on addition of histamine. If at this point the specific antigen is added to the bath the uterus will contract (X).

The so-called antihistamine drugs, which in small amount will prevent histamine anaphylactoid shock (Y), and in large amount will prevent allergic anaphylactic shock (Z), may exert their effect by action on body enzymes. The action of mono-amino oxidase, which inactivates epinephrine, is nullified by the antihistamine drugs.

Proteolysis occurs in anaphylactic shock due to an increase in protease activity (Aa). Decalcification of antisera increases protease activity also (Bb).

Cortisone pretreatment is ineffective in preventing histamine-induced immediate reactions, either general or local (Cc).

Plasma Antibody Reactions Developing Hours Later (Table 4)

Additional reactions occur in the presence of plasma antibody and antigen. Since they occur long after the initial 15 minutes required for

TABLE 3

Role of Histamine

	Animal	Preparation	Challenge	Reaction
V	1, 2, 3, 4		Histamine circ.	Anaphylactoid shock (adrenalin changed by mono-amino-oxidase)
W	1, 2, 3, 4		Toxins, venom, peptone, trypsin, circ.	Anaphylactoid shock
X	G. pig uterus 1, 2, 3, 4	Bath. "Poison" by histamine, repeatedly, large quantity	Histamine bath	Relaxation
			Peptone bath, or venom bath	Contraction
	Sensitized G. pig uterus 1, 2, 3, 4	Bath. "Poison" by histamine, repeatedly, large quantity	Antigen bath	Contraction
	Sensitized G. pig lung 1, 2, 3, 4	Bath. Add antigen (minute amount histamine liberated)	Rat uterus (hist. insensitive) to same bath	Rat uterus contracts
Y	G. pig 1, 2, 3, 4	Antihistamine, small amount (mono-amino-oxidase inhibited)	Histamine circ.	None
	Rabbit 1, 2, 3, 4		Histamine to uterus in bath	None
			Histamine circ.	None
Z	G. pig 1, 2, 3, 4	Actively sensitize. Give large amount antihistamine	Antigen circ.	None
Aa	G. pig 1, 2, 3, 4	Actively sensitize	Antigen	Anaphylactic shock. Proteolysis, due to increase in protease, due to 1) Increase pro-enzyme, or 2) Decrease anti-protease
Bb	Antiserum 1, 2, 3, 4	Decalcify (removes antiprotease)	Antigen	Increase in protease
	Serum		Peptone	
Cc	Man 26	Treat ACTH or cortisone	Histamine or Mecholyl	"Bronchospastic" reaction
	Asthmatic man 26			

complete union of antigen and plasma antibody, they are different from the plasma antibody reactions described above. These additional reactions can hardly be considered to be the direct result of antigen-antibody union,

TABLE 4

Plasma Antibody Reactions Developing Hours Later

	Animal	Preparation	Challenge	Reaction
Dd	Rabbit 27	Arthus sensitized actively, then treat ACTH or cortisone	Antigen skin	None
	Rabbit 27	Arthus sensitized passively, then treat ACTH or cortisone	Antigen skin	Arthus reaction
	Rabbit 1, 2, 3, 4	Arthus sensitization	Antigen skin	½ *hour:* dynamic vascular *1 hour:* a) Edema (swelling fibrils) b) WBC stick endothelium c) Vessel compression *24 hours:* a) Adventit. edema, inflam. b) Fibrinoid degeneration c) Arteriolar necrosis d) Hemorrhage
	Rabbit 23	Actively sensitized, small amt. circ. antibody	Antigen skin	Small transient reaction
	Rabbit 23	Actively sensitized, large amt. circ. antibody	Antigen skin	Pronounced Arthus
Ee	G. pig 28 28a 29 30	Actively sensitized	Antigen into: 1) Mesenteric vein 2) Knee 3) Foot 4) Renal artery	1) Liver necrosis 2) Arthritis 3) Arthritis 4) Unilateral glomerulonephritis
Ff	Rabbit 31		Shwartzman filtrate skin	1) Polys around venules locally 2) Lactic acid locally (aerobic glycolysis) 3) Endothelium sensitized to tissue proteases??
	Rabbit 31	Shwartzman filtrate into skin, wait 8 to 12 hours	Shwartzman filtrate intravenous	1) Leukopenia (anaphyl.) 2) WBC+platelet clumps (Arthus) 3) Clumps sequestered in a) Lungs (anaphyl.) b) Liver, spleen and "damaged" endothel. 4) In "sensitized" area: thrombus, occlusion, vessel necrosis, disintegration, hemorrhage (Arthus)
	Rabbit skin 32	*S. marcescens* polysaccharide filtr., wait 8 to 32 hours	*S. marcescens* polysacch. filtr. intravenous	Necrosis and hemorrhage at prepared site

TABLE 4—*Continued*

	Animal	Preparation	Challenge	Reaction
Gg	Rabbit 33	Mening. toxin I.V.	Mening. toxin I.V.	1) Glomer. intracapillary masses 2) Renal cortical necrosis
Hh	Rabbit 34	Mening. toxin I.V., then give heparin	Mening. toxin I.V.	None
Ii	Rabbit 1, 2, 3, 4	Bact. filtrate "A" skin, wait 8 to 32 hours	Bact. filtrate "A" I.V. or Bact. filtrate "B" I.V. or I.V. starch, agar or washed antigen-antibody precipitate	Hemorrhage and necrosis at prepared site in few hours
Jj	Rabbit 32	1. Active immunized. 2. Bact. filtrate skin, wait 8 to 32 hours	I.V. specific antigen	Shwartzman reaction at prepared site
	Rabbit 1, 2, 3, 4	Active immunized	Shwartzman filtrate plus antigen skin	Magnification Arthus reaction
	Rabbit 1, 2, 3, 4	1. Bact. filtr. I.V. 2. Treat cortisone	Bact. filtrate I.V.	Magnification Shwartzman reaction kidneys
	Rabbit 1, 2, 3, 4	Cortisone treat.	Bact. filtrate I.V.	Renal cortical necrosis

and therefore histamine or related substances can probably be dismissed as of any major importance here.

The Arthus reaction is representative of these additional reactions (Dd). It can be produced only if the level of plasma antibody is high. If the level of plasma antibody is below a certain critical level, and if the antigen is injected locally in an appropriate animal, there will be immediate local dynamic vascular changes but no subsequent Arthus reaction. If local union of antigen with antibody were the mechanism for production of the Arthus reaction, we should expect to see it in the above preparation. Obviously, since the Arthus reaction did not occur, there must be another explanation for its production. Since it can be produced in an animal with antibody titer above the critical level, there is perhaps the factor of large masses of antibody agglutinated or flocculated by the antigen, operating in the production of the lesion. This large mass, by its physical presence, or perhaps by some more subtle mechanism, may be sufficient to explain the occurrence of the Arthus reaction.

The reaction itself consists of necrosis and hemorrhage, in addition to the edema and cellular infiltration that are part of the local immediate reaction. The hemorrhage and necrosis do not appear for many hours, and are not fully developed for 24 hours (Dd).

Corticotropin and cortisone will abolish the ability to develop an Arthus

reaction only through their influence on plasma antibody formation. When as a result of cortisone therapy the plasma antibody titer has fallen below the critical level, no Arthus reaction can be produced. Pretreatment with cortisone will not abolish the ability of a passively sensitized animal to develop an Arthus reaction, since cortisone, although it does abolish antibody production eventually, does not accelerate antibody excretion (Dd).

Here, then, is a reaction dependent on antigen-antibody union but apparently not related to the simple act of union. Rather, it is related to some other factor dependent on large amounts of plasma antibody, and this is probably the agglutination of large masses of plasma antibody (Ee).

An identical tissue reaction, the Shwartzman reaction, can be produced in the absence of plasma antibody (Ff). This in itself suggests that the mechanism of the Arthus reaction is not the act of union of antigen with antibody. The mechanism of the local Shwartzman reaction is not well understood, but studies have thrown light on the mechanism of the systemic Shwartzman reaction. In this latter reaction both injections are given intravenously (Gg). The kidney is the site of the most profound changes, and the presence of eosinophilic homogeneous masses in the lumens of the glomerular capillaries is the most striking basic lesion; an equally striking but secondary lesion is tubular cortical necrosis and hemorrhage. If heparin is administered between the two intravenous injections of the meningococcus toxin, there is an absence of occurrence of the intracapillary masses and of the expected tubular cortical necrosis and hemorrhage (Hh).

In the above experiment heparin has apparently prevented the occurrence of the entire reaction by preventing the formation of the basic intracapillary masses. It would appear, therefore, that intravascular masses are responsible for the lesions of the systemic Shwartzman reaction. If this is analogous to the local Shwartzman reaction, where the only difference lies in the route of administration of the preparatory injection, it too might then be dependent on the presence of intravascular masses.

Since the pathology of the Arthus reaction is the same as that of the local Shwartzman reaction, this would suggest that the basis of the Arthus reaction too may well be the presence of intravascular masses, and here agglutinated antibody would perhaps be the substance producing the mass.

Not only may the Shwartzman reaction be produced by using different bacterial filtrates for preparation and challenge, but also starch and agar may be used successfully as challenging agents when preparation has been with bacterial filtrate (Ii). Moreover, the close relationship existing between the Shwartzman and the Arthus reactions can be inferred by preparing the subject with bacterial filtrate and challenging successfully with washed antigen-antibody precipitate (Ii). Also, if the animal has been specifically sensitized prior to local Shwartzman preparation, successful challenge can be performed with the specific antigen alone, given intravenously (Jj), and the resultant reaction is a local Shwartzman phenomenon.

Cortisone appears to magnify the Shwartzman reaction (Jj). One in-

vestigator has observed that cortisone treatment renders an experimental animal so susceptible that the lesions of the generalized Shwartzman reaction may be produced simply by giving a single intravenous injection of an appropriate bacterial filtrate (Jj).

Lymphocyte Antibody Formation (Table 5)

This antibody is immunologically active only when present within healthy, living white blood cells (Kk). It is thought that only mononuclear cells are capable of containing this antibody, and that the lymphocyte is probably the mononuclear cell involved (Ll).

Lymphocyte antibody appears to be formed when antigen is slowly liberated in conjunction with a focal tissue reaction (Mm).

Table 5

Lymphocyte Antibody Formation

	Animal	Preparation	Challenge	Reaction
Kk	G. pig 35	1) Active tuberculosis 2) WBC tissue culture	Tuberculin tissue culture	Cells damaged
Ll	Man 36 36a 37	Lymphocytes into skin a) From tuberculin-sensitive man	Tuberculin skin	Delayed
		b) From streptococcal-sensitive man	Strep. extract a) Skin b) Subcutaneous	a) Delayed local b) Delayed systemic
		As above, except that a) Cells extracted, or b) Cells damaged	Antigen skin	None
Mm	Man 35 38	Any infection or intracutaneous injection		Bact. antigen slowly liberated a) Focal tissue reaction b) Bact. antigen handled differently 1) Formation special antibody: lymphocyte affinity
	Man 1, 2, 3, 4	As above		1) Delayed skin sensitivity 2) Delayed systemic sensitivity
Nn	G. pig 39	Intraperitoneally cells from g. pig a) Tuberculosis	a) Tuberculin 1) Skin 2) Circulation	1) Delayed local 2) Delayed systemic
		b) Brucellosis	b) Brucell. extract 1) Skin 2) Circulation	1) Delayed local 2) Delayed systemic
	G. pig 40, 55	WBC from epidermally sensitized	Antigen	Delayed

TABLE 5—*Continued*

	Animal	Preparation	Challenge	Reaction
Oo	G. pig 43	Into skin organ from Mellitine sensitized animal, +Mellitine		Exudative
	G. pig 43a 44	Into skin exudate from above	Mellitine skin	Delayed (sensitivity transferred by WBC)
	G. pig 45, 46	Killed tubercle bacilli plus paraffin oil systemically		
	G. pig 45, 46	Cells from above preparation intraperitoneally	Tuberculin 1) Skin	1) Delayed local
			2) Circulation	2) Delayed systemic
Pp	1, 2, 3, 4	Into skin killed tuberc. bacilli +Paraffin oil +Homolog. brain	Extract of brain or cord into skin	Delayed local
	1, 2, 3, 4	Erythrocyte stroma +Freund adjuv. +Drug		Delayed sensitivity to drug established
	G. pig 44	Killed tubercle bacilli + picryl chloride intraperitoneally	Picryl chloride patch test skin	Dermatitis venenata locally

	Guinea pig	Lymphocytes	Normal plasma		Tuberculous plasma	Complement	Tuberculin	Dissolution of lymphocytes
Qq	47 Sensitized to give positive tuberculin test	+	+	Conditioned plasma				
	Sensitized to give positive tuberculin test	+	+			+	+	Slow
	Active tuberculosis	+					+	Prompt
	Normal	+			+	+	+	Prompt
	Normal	+		+		+	+	Prompt

Lymphocyte antibody is concerned with classic delayed or tuberculin-type reaction. The transfer from one animal to another of this delayed type of allergy can be accomplished by using lymphocytes from an actively sensitized experimental animal or patient, as well as those from an experimental animal with active disease (Nn).

If such sensitized cells are harvested and injected into a normal animal of the same species the recipient becomes passively sensitized. This passive sensitization is general, suggesting that the recipient's lymphocytes have

themselves become sensitized, since, under appropriate conditions, the recipient when challenged can be thrown into a systemic reaction of the delayed type (Oo).

Experimentally, homologous tissues or drugs can produce delayed sensitivity states if they are mixed with appropriate adjuvants prior to injection. The hypersensitivity produced is then specific for the injected organ or drug (Pp).

In a series of experiments it has been found that lymphocyte antibody diffuses in and out between mononuclear cells and plasma. Thus the plasma from an animal with this type of sensitization can sensitize normal cells, and sensitized cells can sensitize normal plasma. In the plasma, however, the antibody is immunologically inert (Qq).

In the normal animal the tissues react to the injection of antigen in the

TABLE 6

Lymphocyte Antibody Reactions

	Animal	Preparation	Challenge	Reaction
Rr	G. pig 48		Agar, silica or tubercle bacilli into skin	Locally polymorphs for 2 days
Ss	Man 49	Primula skin repeatedly	Primula skin	Dermatitis venenata
	G. pig 1, 2, 3, 4	Primula skin for 5 to 20 days	Primula skin	Dermatitis venenata
		Primula skin. Skin generally sensitized	Primula distant site	Dermatitis venenata
	G. pig 1, 2, 3, 4	Primula skin continuously at different sites		Day 7 flare old sites: new antibody reacting with fixed antigen
Tt	Man G. pig 1, 2, 3, 4	Generalized tuberculosis	Tuberc. prot. skin	1) Edema + polys first 6 hours 2) Then perivascular mononuclears, histiocytes and undiff. mast cells
Uu	Man 51		GP. A streptococ. extract skin	45% Local delayed
	Rabbit 52	*Streptococcus viridans* into skin	Skin or conjunct. sac 1) Living strep. 2) Strep. polysacch. 3) Strep. nucleoprot.	Delayed. Not transferable with plasma
Ww	G. pig and rabbit 53	1) Tuberculosis 2) Spleen to tissue culture	Tuberculin to spleen-culture	Cells damaged

TABLE 6—*Continued*

Animal		Preparation	Challenge	Reaction
Vv	Man 54	1) Cowpox skin 2) Primary reaction	Heated cowpox skin	Delayed
Xx	Man 55	Transfer skin to epidermally sensitized twin	Antigen to transplant	Delayed
Xx	Epidermally sensitized man 55	Transfer skin to normal twin	Antigen to transplant	None
Yy	Man 56, 57	1) Tuberculin sensit. 2) Treat ACTH, cortisone	Tuberculin skin	Abolished or diminished
Yy	Man 1, 2, 3, 4	As above	As above	Rebound delayed reaction if treatment stopped within 3 weeks
Zz	1, 2, 3, 4	1) Tuberculin sensit. 2) Treat tuberculin		Lympholysis and desensitization
Zz	Man or G. pig 58, 59	Tuberculosis	1) One large dose tuberc. protein	1) a. Severe constitutional b. Desensitized
			2) Repeated small doses tub. prot.	2) May desensitize
			3) Repeated large doses P.P.D.	3) Desensitized. Skin reacts normally to dye spread
Zz	1, 2, 3, 4	1) Tuberculin sensit. 2) Treat ACTH, cortisone		Lympholysis and desensitization

same way that they react to foreign substances of any type, by calling forth polymorphonuclear leukocytes to the site of the injected material (Rr).

LYMPHOCYTE ANTIBODY REACTIONS (Table 6)

These reactions develop slowly after challenge, and are classically referred to as delayed or tuberculin-type reactions. Dermatitis venenata and the allergy associated with tuberculosis and brucellosis are the outstanding examples (Ss).

Immediately after the introduction of challenging antigen there is infiltration with polymorphonuclear leukocytes, just as there is in the normal animal (Tt). In the lymphocyte-antibody sensitized animal, however, mononuclear cells appear after six hours.

This type of allergic reaction occurs in association with infection with a great many bacteria (Uu) and at least one virus (Vv). It is possible that it may also exist in a wide number of diseases, including those clinical allergic reactions that occur 18 to 36 hours after challenge.

In the animal so sensitized a particular body focus is constantly the site

of each newly induced reaction. When this type of allergy arises spontaneously, or as the result of experimentally induced disease, the particular "sensitized" locus is determined by the nature of the spontaneous disease. Also, if tissue cells from an animal with this type of allergy are artificially cultured, and if the antigen is added to the culture, the tissue cells will be damaged (Ww).

The above strongly suggests that fixed tissue antibodies exist as the mechanism of this type of allergic reaction. There is evidence to indicate, however, that this may be more apparent than real, and that in actual fact the allergy is generalized, dependent primarily on lymphocyte antibody and not on permanently fixed tissue antibody. Transplantation of a reactive tissue to a normal twin soon resulted in loss of reactivity, and transplanting normal tissue to a twin so sensitized soon resulted in reactivity of the formerly normal tissue (Xx).

This type of allergic reaction is very effectively abolished or prevented by treatment with corticotropin or cortisone (Yy). In certain instances desensitization, with abolishment of the capacity to develop this type of reaction, is effective when an extract of the antigen is injected into the animal (Zz). It is thought by some investigators that lympholysis is effected by both types of therapy, and may therefore be the mechanism by which this hypersensitivity is lost (Zz).

Plasma and Lymphocyte Antibody Formation (Table 7)

In those states in which lymphocyte antibody is formed, plasma antibody against the same antigen is also frequently formed (Aaa). The plasma antibody, however, appears to have nothing to do with the delayed type of

Table 7

Plasma and Lymphocyte Antibody Formation

	Animal	Preparation	Lymphocyte Antibody	Plasma Antibody	
				Present	Significance
	G. pig 1, 2, 3, 4	Tuberculosis	Always	1) Anti-carbohydr. 2) Anti-protein	Cannot transfer Delayed allergy
	1, 2, 3, 4	Spontaneous infection	Yes	Often	
	1, 2, 3, 4	Bact. protein	Yes	Often	
Aaa	G. pig 1, 2, 3, 4	Killed bact. cells + paraffin	Always	Often	
	G. pig 1, 2, 3, 4	Tuberculin + wax fraction	Always	Often	
	1, 2, 3, 4	Focal tissue reaction + sensitizing contact	Always	Sometimes	

reaction. The plasma, with its own antibody, when transferred to a normal animal, does not passively transfer the delayed type of allergy.

Plasma and Lymphocyte Antibody Reactions (Table 8)

Living antigens, by reason of the complexity of the reactions they call forth in the host, are usually associated with the production of specific lymphocyte antibody. Apparently the polysaccharide content of the bacterium, virus or fungus determines whether there will be simultaneous development of specific plasma antibody (Bbb). When plasma antibody is formed under these circumstances, it exhibits on union with the antigen the classic reactions of plasma antibody, including anaphylactic shock, the Arthus reaction, and the ability to sensitize passively a normal recipient for similar reactions (Ccc).

The level of plasma antibody so formed has nothing to do with the severity or size of the delayed type of reaction. Successful desensitization of the delayed type of reactability has no effect on the level of plasma antibody (Ddd).

Living antigens are not the only ones capable of producing both types of antibody. Dual antibody can readily be produced against egg white when this antigen is injected into an active tuberculous lesion (Eee). It is then possible, on appropriate challenge, to obtain both immediate and delayed reactions to egg white.

One investigator has found that lymphocytes from a donor with delayed type of allergy, when transferred to a normal recipient, are capable of giving rise to production of active plasma antibody, rendering the recipient anaphylactically sensitive (Fff). Since no antigen was detected in the transferred material, this experiment would seem to indicate that plasma antibody may arise from an activity of lymphocyte antibody. However, another investigator has found that tagged antigen can be shown to exist within tissue cells, including circulating cells, months after a single injection (Fff). Therefore, it is not certain that the production of active plasma antibody by sensitized lymphocytes is due to a passive and not an active process.

These experiments do demonstrate the close relationship that exists between the two basic types of allergy. In clinical allergic disease, not only may it be difficult to distinguish between the two types of allergic reactions in a particular patient's disease, but also the mere demonstration of the presence of plasma antibody to a specific antigen does not exclude the possibility of that antigen's reaction with lymphocyte antibody being the mechanism of production of the observed clinical disease.

Further evidence of the similarity between plasma and lymphocyte antibody reactions is the occurrence of hemorrhage along the needle track and in serous cavities when the tuberculous animal is injected with a large volume of old tuberculin. This hemorrhage, which occurs within several hours, is reminiscent of the hemorrhage of the Arthus reaction (Ggg). Also, when

TABLE 8

Plasma and Lymphocyte Antibody Reactions

	Animal	Preparation	Challenge	Reaction
Bbb	Man 1, 2, 3, 4	High specific polysaccharide containing a) Bacteria b) Fungi c) Viruses		Lymphocyte type almost constantly Plasma type frequently (clinically impossible to decide)
Ccc	G. pig 60	Epidermally sensitized (circulat. antibody sometimes formed)	Drug + prot. I.V.	Anaphylactic shock. Serum will transfer immediate type reactability
	G. pig 61	Horse serum + lanolin + killed tubercle bac. + paraffin oil	Horse serum into skin	1) Necrotic (lymphocyte type) 2) Arthus (plasma type)
	G. pig 62, 63	Killed tubercle bac. + paraffin oil	Water extract I.V.	1) Anaphylactic shock often 2) Positive complem. fixation
	G. pig 64, 65	Lymphocytes (from tuberc. sensit. g. pig) into skin	Tuberculin 1) Intraperit. 2) Into distant skin	1) Anaphylactic shock 2) Local delayed type resembling Shwartzman
Ddd	G. pig 1, 2, 3, 4	1. Sensitize tuberc. bacilli 2. If level of circulating antibody formed is		
		a) Small	Tuberculin skin	Delayed, large or small
		b) Large	Tuberculin skin	Delayed, large or small
		c) Large	Tuberculin skin	1) No local reaction 2) High level circulating antibody persists
		then desensitize with large amt. tuberculin		
Eee	G. pig 66, 67	1. Active tuberculosis 2. Egg white into local lesion (where histiocytes, lymphocytes predominate)	Tuberculin skin	Delayed local
			Egg white I.V.	Anaphylactic shock
			Egg white skin	Delayed local
Fff	G. pig 61, 68	Picryl chloride + adjuvant	Antigen skin	Delayed local
	G. pig 68, 69	Cells from above epidermally sensitized	Antigen systemic	Immediate vascular, not related to epidermal sensitization
	Mouse 69a	1. Inject whole blood or tissues from mouse that had been injected once with antigen one to three months before	Antiserum (from actively sensitized rabbit)	Dynamic vascular reactions, as in anaphylaxis
Ggg	G. pig 1, 2, 3, 4	1. Virulent tuber. bacilli 2. Wait two weeks	Dead organisms skin	Local inflam., slough
			O. T. subcutaneous	1) Lethal delayed shock 2) Hemorrhage (needle track, serous cavities) 3) Tubercles dense WBC infiltration
Hhh	G. pig, Tuberculosis 70	1. Tuberculin skin 2. Wait fully developed	I.V. different Bacterial filtrate	Shwartzman at site of tuberculin reaction

a tuberculin skin reaction is fully developed, intravenous administration of a Shwartzman bacterial filtrate gives rise to a hemorrhagic, necrotic reaction superimposed upon the tuberculin skin reaction (Hhh).

Fixed Vascular Reactions Developing Days Later (Table 9)

Periarteritis nodosa is the most representative member of this group. The fact that these lesions are not fully developed for from five to seven days after challenge removes them from the group of 15 minute reversible vascular phenomena due to act of union of antigen with antibody. Since they are hardly apparent at all 24 hours after challenge they probably fall into a different group from the Arthus type of reaction.

Cortisone pretreatment effectively prevents the occurrence of these lesions. With cortisone treatment the level of plasma antibody is slightly decreased, as would be expected, but is not appreciably lower than the level

Table 9

Fixed Vascular Reactions Developing Days Later

Animal	Preparation	Challenge	Reaction
Iii { Rabbit 27, 71	1) Sensitize horse serum 2) Precipitin formed 3) Treat with cortisone	Horse serum I.V.	1) Periarteritis suppressed 2) Precipitin level unchanged
Jjj { Rabbit 72	Passively sensitized with rabbit antiserum	Antigen I.V.	Sacrificed 24 hours later: pulmonary arteriolar cellular infiltration
Kkk { Rabbit 73	1) Treat with cortisone 2) Passively sensitize with rabbit antiserum 3) Continue cortisone	Antigen I.V.	Suppression of pulmonary arteriolar reaction

in a control group of untreated animals which developed expected lesions of periarteritis nodosa (Iii). At the present time it appears that the effect of cortisone here is not due primarily to its effect on plasma antibody level. If later investigation confirms this, it will be inferred that the immunogenesis of the lesions of periarteritis nodosa is different from the immunogenesis of the Arthus reaction.

Since cortisone, as shown in previous sections of this review, neither accelerates antibody excretion (Dd) nor prevents deposition of antigen-antibody masses (Jj), it would appear that its effect on prevention of experimental periarteritis nodosa is mediated through some other mechanism. It is possible that lymphocyte antibody may be concerned with the lesions, and that plasma antibody, which is constantly present, may be coincidental to the development of the lesions, or at least may operate in some manner not at present understood.

One group of investigators, in inquiring into the immunogenesis of this disease, worked with passively sensitized animals. They challenged these

animals, sacrificing them 24 hours later (Jjj). The pulmonary arterioles and small arteries showed extensive infiltration with leukocytes around and in the walls. Since these lesions were present 24 hours after challenge, their interpretation as lesions of true periarteritis nodosa is open to some question. Under the conditions of the experiment one might expect to observe an Arthus-like effect at the time of sacrifice. However, further studies done by this group (Kkk) demonstrated that cortisone was effective in inhibiting the production of these lesions; an Arthus reaction could not be inhibited by this method. It is possible that the observed lesions may have been the normergic pulmonary arteriolar mesenchymal response, although injection of an indifferent antigen was not productive of similar lesions. It would appear that the problem of the exact rôle of plasma antibody in the production of the lesions of periarteritis is at present unsolved.

Clinical Correlation

Some clinical diseases are always due to the same immunologic mechanism. Dermatitis venenata is always due to lymphocyte antibody. Immediate shock following injection of an antigen is always due to plasma antibody acting immediately with its antigen to produce a "histamine-like" or protease effect. Local hemorrhage and necrosis at the site of re-injection of an antigen, developing the following day, are always due to plasma antibody, in high level, uniting with its antigen to produce, perhaps, intravascular masses hours later. This last reaction may also be produced by masses other than antibody, as exemplified by the Shwartzman reaction.

There are other clinical diseases not due to the same immunologic mechanism in every patient, or even in the same patient every time. Bronchial asthma, allergic rhinitis and urticaria are examples of this large group. In the past it was widely believed that these diseases were invariably due to "histamine-like" phenomena, with the implication that the clinical reaction arose as the result of the immediate effect of antigen uniting with plasma antibody. The failure of the antihistaminic drugs, and the success of cortisone in controlling a large segment of these diseases, require us to visualize a different immunogenesis.

Wherever corticotropin or cortisone is effective in abolishing or suppressing an allergic disease after a few days of therapy, it would appear probable that the immune reaction of the disease must either have been due to lymphocyte antibody, or else have been related to the immunogenesis of fixed vascular reactions developing days after challenge. In this latter group, which includes periarteritis nodosa, the immunogenesis is poorly understood at present.

When cortisone therapy becomes effective only after prolonged administration it is probable that plasma antibody formation has eventually been suppressed, with resultant fall in its plasma level, and that the disease was probably due to one of the two actions of plasma antibody, either the

immediate or the 24 hour type. The successful treatment of some hemolytic diseases with cortisone seems to have put them in this class.

The mere demonstration of specific plasma antibody does not prove that plasma antibody is responsible for the observed reaction. It has been seen in this review that some antigens may, under appropriate circumstances, give rise to both plasma and lymphocyte antibody. In such a preparation either a tuberculin-like or an anaphylactic type of reaction may be produced. Therefore, a clinical tuberculin-like reaction could exist in the presence of incidental plasma antibody against the same antigen. Classic skin testing would disclose the plasma antibody's existence but would not prove its significance.

In such a case, however, skin testing would detect the antigen. In other cases, where only a lymphocyte antibody exists, skin testing with negative immediate results, if thoughtfully evaluated by correlating the suspected significance of this antigen in the production of the clinical reaction, would help to classify the immune mechanism as that due to lymphocyte antibody.

Summary

It may be stated that the approach of the attending physician to these problems should be flexible rather than rigid. It is well to realize that a number of immune mechanisms operate in the production of allergic reactions, and that one of them is operating to produce the individual patient's disease. Moreover, the correct diagnosis of the name of this disease does not carry with it an identification of the immune mechanism, for the same disease may be the result of different immunologic mechanisms in different patients.

Ideal management of the patient with an allergic reaction requires that the diagnosis be extended beyond the confines of the diagnoses listed in the standard nomenclature of disease. It would be desirable to be able to record that the patient suffers from a specific disease of a particular immunogenetic type, and then if possible to name the antigen which precipitated the reaction.

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STUDY OF TOTAL RED CELL VOLUME AND ERYTHROCYTE SURVIVAL USING RADIOACTIVE CHROMIUM IN PATIENTS WITH ADVANCED PULMONARY TUBERCULOSIS *

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Radioactive chromium in sodium chromate is adsorbed firmly on the hemoglobin of intact red cells, thereby tagging the cells. Such red cells were used by Sterling and Gray to measure total red cell volume,[1] and by Ebaugh, Emerson and Ross to study the survival of erythrocytes in vivo.[2]

In the past, the hemolytic element of the anemia of chronic infections has been investigated only by the measurement of pigment excretion, which was found to be normal.[3] No studies of erythrocyte lifespan in patients with tuberculosis have been reported. Berlin [4] has measured red cell volume in patients with tuberculosis, using radioactive phosphorus, and several workers have reported plasma volume determinations,[5] but no reports have appeared on measurement of red cell volume in tuberculosis by the Cr^{51} method. A study was therefore undertaken to measure both red cell volume and red cell survival in a large group of patients with advanced active pulmonary tuberculosis, using radioactive chromium.

The radioactive chromium method for study of erythrocyte lifespan has several advantages over the Ashby technic of differential agglutination. The method is simple and accurate, and eliminates the dangers of transfusion by using the subject's own red cells. The chief disadvantage of the Cr^{51} technic for red cell survival is that the pattern of normal survival is not a straight line, as in the Ashby method, but is curved due to the elution of some of the chromium from its hemoglobin bond. The normal Cr^{51} curve, then, is composed of the two components: (a) elution of chromium from the cells, and (b) red cell destruction. For this reason, most investigators have reported their results not in terms of average survival of tagged red cells, but rather in terms of half-life of radioactivity in the circulating blood, or they have simply shown the curves. In the normal subjects the biologic half-life has been reported to vary from 25 to 40 days.[2, 6, 7]

Materials and Methods

All patients studied had advanced active pulmonary tuberculosis, and many had a moderate anemia as revealed by hematocrit values. Approxi-

* Received for publication August 19, 1954.

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mately 30 ml. of blood were drawn from each subject and placed in a sterile, glass-stoppered 50-ml. centrifuge flask containing 6 ml. of acid citrate dextrose solution and 100 microcuries of $Na_2Cr^{51}O_4$ (Abbott). The mixture was allowed to incubate for an hour at room temperature. The bottle was filled with sterile saline, the mixture was centrifuged for 10 minutes at 2,000 rpm in a standard International centrifuge, and the supernatant plasma and saline were removed. The packed cells were resuspended by refilling the bottle with saline and 30 ml. injected into the subject. An initial blood sample was taken after 15 to 30 minutes for the blood volume determination, and subsequent samples were taken for cell survival after two to three days, then at weekly intervals for 10 weeks.

Radioactivity was measured in a well-type scintillation counter. The standards for the blood volume measurements were prepared by diluting in 5 ml. of distilled water, 0.02 ml. of the cell suspension prepared for injection. The same calibrated pipet was used in all subjects, and duplicate standards agreed within 3%. Red cell volumes were computed as follows:

$$\frac{\text{ct. of std.} \times \text{dil'n of std.}}{\text{count of sample}} \times \text{ml. of cells injected} \times \text{hematocrit} \times .98\ *$$

For the determination of red cell survival five milliliter blood samples were counted simultaneously with the initial post-injection sample, and residual radioactivity was expressed as a percentage of the initial sample. The counting time was sufficient to insure a random sampling error of less than 2% in the early samples and less than 5% in most of the later samples.

Results and Discussion

A. Blood Volume: Satisfactory blood volumes were obtained in 38 patients (11 women and 27 men). The red cell volumes, expressed as ml./Kg. of body weight, are plotted in figure 1. The solid line (through the graph) represents the anticipated hematocrit value if decrease in red cell volume were completely compensated by an increased plasma volume, leaving the total blood volume unchanged. This line is computed from a point derived from the mean red cell volume and mean hematocrit of 20 normal male subjects, with the extension of a line through this point to 0. We have no values for normal women, but Berlin's data [8] give a similar line for women. In figure 1, 23 ml./Kg. body weight has been arbitrarily chosen as the level of anemia. If the patients with low total red cell volumes had an increase in plasma volumes to compensate for the loss of red cell mass, the points would fall in a range in both sides of the line.

The data in figure 1 reveal that anemia was more common and more severe in this group of patients than was anticipated from the hematocrit values. A decrease in total blood volume is indicated by the fact that, of the 19 subjects with red cell volumes below 23 ml./Kg., only two were above the theoretic line of unchanged blood volume. In the nonanemic

* Correction for plasma trapping.

group (red blood cell volume above 23 ml./Kg.), the blood volume appears to be normal in most instances.

Our data indicate that in patients with severe tuberculosis a normal hematocrit may mask a true anemia when plasma volume fails to expand enough to compensate for the diminished red cell mass, and even in patients with low hematocrits the severity of the anemia may be obscured. These results are in essential agreement with those of Berlin [4] using P^{32}, and of

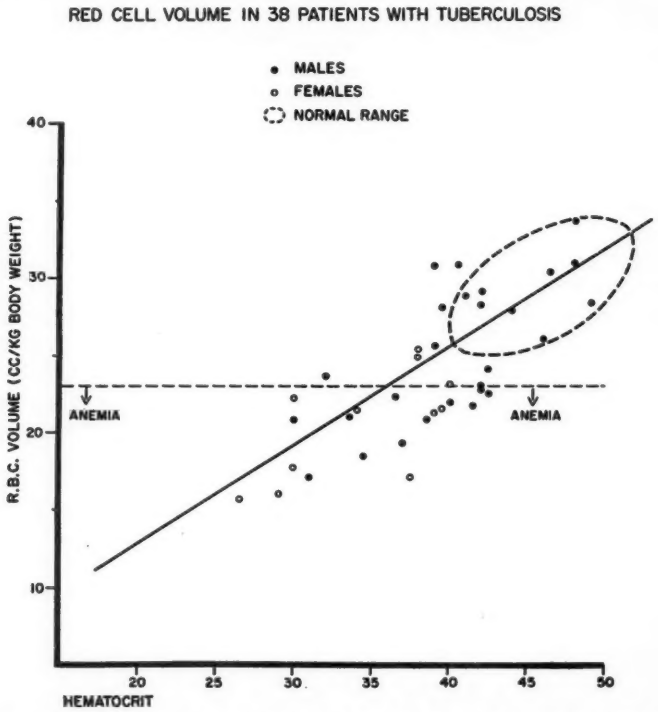

FIG. 1. Red cell volume and hematocrits of 38 patients with tuberculosis. The sloping line represents the theoretic red cell mass and hematocrit if total blood volume remained normal in anemia. The broken horizontal line at 23 ml./Kg. was arbitrarily chosen as the level of anemia.

von Porat [5] using Evans blue dye, but this interpretation of masked anemia is worthy of emphasis. Masked anemia and low total blood volume may add to the risk involved when major surgical procedures are performed on such subjects.

Our results and those of Berlin [4] have been calculated on the basis of body weight, despite the fact that this group of patients was markedly emaciated. Our male subjects had an average weight of only 58 Kg. In emaciated individuals such as these it is difficult to decide how to relate

blood volume figures. In relatively acute malnutrition, plasma volume does not change and hematocrits are only slightly decreased,[9] so that calculation of blood volume on the basis of the emaciation weight gives high values. Studies of chronic emaciation in prisoners-of-war revealed little change in total plasma volume but decreased red cell volumes.[10, 11] If our data were

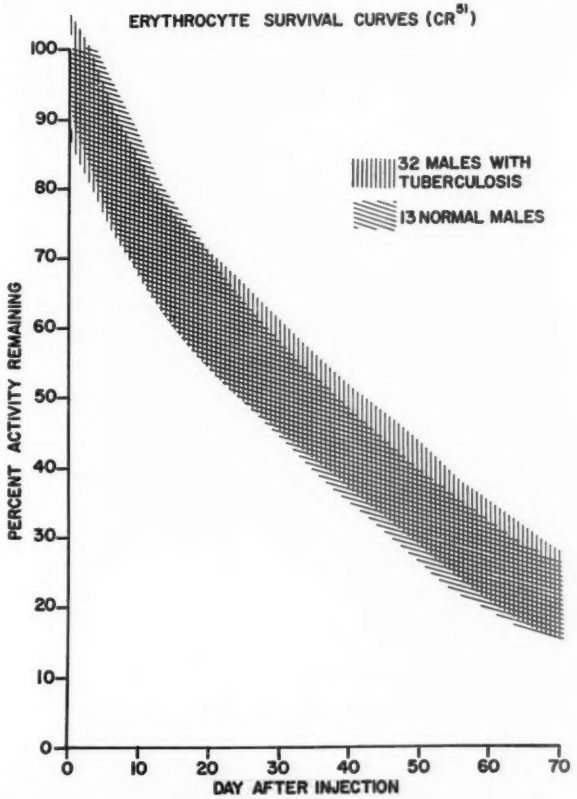

FIG. 2. Comparison of survival curves of normal and tuberculous men.

expressed in terms of height, surface area or normal weight, deviations below the normal would be more marked.

Two of our patients and two of Berlin's patients had rather high values for red cell mass as related to body weight. Berlin thought his patients had hypervolemia secondary to pulmonary fibrosis despite their normal hematocrits. We feel that our high figures are probably related to cachexia and reflect the inadequacy of body weight as the point of reference, especially in subjects with emaciation.

B. Erythrocyte Lifespan: The results of the studies on erythrocyte lifespan are summarized in figures 2 and 3, except for two subjects who appeared to have a mild hemolytic disease. In figure 2 the Cr^{51} red cell survival curves of 32 men with tuberculosis are superimposed on the curves obtained in 13 normal male subjects. It can be seen that the ranges are

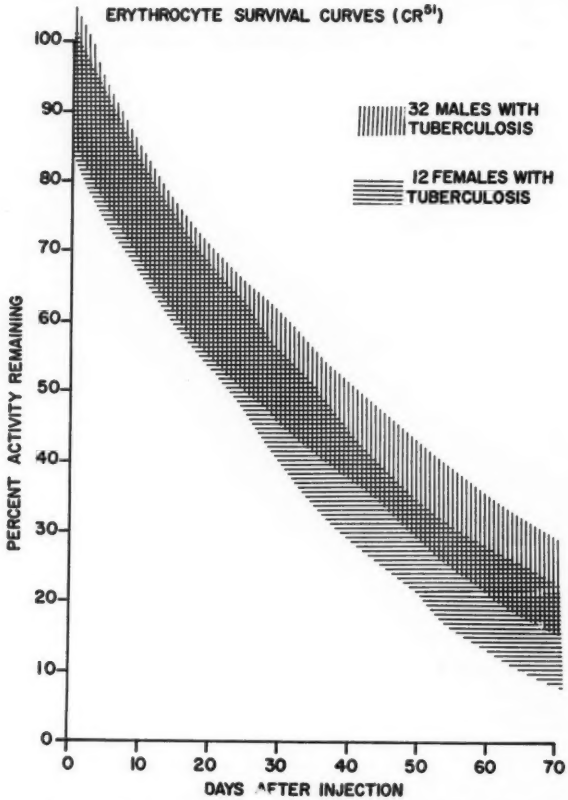

FIG. 3. Comparison of survival curves of tuberculous men and women.

almost identical, with a biologic half-life of 25 to 36 days in the normal and 24 to 42 days in the patients with tuberculosis.

In figure 3 the results obtained in 12 female patients are contrasted with the male patients. The range appears distinctly lower in the women. There are no published data in the literature on Cr^{51} survival curves in normal women, but two groups have reported that Ashby curves in normal women show a minimal hemolytic process associated with the menstrual period.[12, 18] Since only one of our subjects was postmenopausal it is possible

that this mechanism might account for the differences between the male and female patients.

In one woman and one man the red cell survival curves were slightly below the normal range, with a half-life of radioactivity at 20 and 22 days. These two abnormal subjects were very ill and severely anemic. These small differences may not be significant, but Ashby and Cr^{51} curves performed simultaneously on other patients have shown that such small variations of Cr^{51} half-life may be associated with a 60 to 70 day Ashby survival.

Summary

1. Red cell volume studies using radioactive chromium in 38 patients with tuberculosis revealed a red cell mass of less than 23 ml./Kg. of body weight in 19 subjects.

2. In many instances a relatively small plasma volume was present, causing the hematocrit to give a poor index of the degree of anemia.

3. The problem of blood volume in relationship to emaciation is briefly discussed.

4. Red cell lifespan by the Cr^{51} method in 32 men and 12 women with tuberculosis appeared normal, while two subjects possibly showed mild hemolytic disease.

5. Our data indicate that the Cr^{51} survival curves in women are somewhat shorter than in men.

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THE TREATMENT OF RHEUMATOID ARTHRITIS WITH HEXAMETHONIUM CHLORIDE: A PRELIMINARY REPORT*

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An approach to the therapy of rheumatoid arthritis through treatment of the associated vascular disturbance has been used by many investigators, with inconsistent results. In 1930 a most direct and apparently successful approach was used by Rowntree et al.[1] in the performance of lumbar and cervicothoracic sympathectomies in 17 patients with rheumatoid arthritis. The rationale for such treatment lay in the frequently noted vegetative disturbances of abnormal sweating, cyanosis, coldness and tingling in the extremities of patients suffering from rheumatoid arthritis. The results of sympathectomy indicated that there was marked relief of periarticular pain in 12 of the 17 patients operated on. Other investigators were unable to obtain results as good as these in subsequent studies.

These vegetative disturbances have been noted by other investigators,[2,3] but their precise relationship to the etiology or the production of symptoms in this disease is unknown. Studies[4,5] have shown that the circulation of the involved extremities in about 60% of patients with rheumatoid arthritis is abnormal, in that there exists a vasoconstriction of the arterioles and a diminution in the size of the capillaries of the nail-beds. As Hench[6] states, however, the diminished circulation of the extremities is probably not involved in the etiology of rheumatoid arthritis, since this disease is rare in occlusive vascular disease. On the other hand, therapy directed toward improvement of circulation does seem to effect some improvement in the symptoms of rheumatoid arthritis, as in the application of heat,[7] and, less successfully, by the use of vasodilators such as niacin.[8] The application of heat is a two-edged sword in that part of the relief afforded is in its counter-irritant effect. Similarly, it is possible that the good results achieved by sympathectomy were due not only to improved circulation in the extremities but also to the removal of other pain-producing factors. Such pain-producing factors might be akin to those found in the reflex sympathetic dystrophies, such as causalgia and the shoulder-hand syndrome. It is certainly true that the end results of rheumatoid arthritis and the shoulder-hand syndrome present similar patterns. In the acute forms, periarthritis occurs in both, and the two diagnoses can be easily confused. In the chronic forms, atrophy of the muscles, stiffness of the fingers with flexion deformity, de-

* Received for publication June 14, 1954. Presented before the New England Rheumatism Society, Annual Meeting, May 21, 1954.
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mineralization of bone and shiny atrophic skin are signs common to both. Therefore, it is possible that the symptoms and subsequent trophic changes in rheumatoid arthritis might have a similar origin and be ameliorated by treatment successfully used in the reflex sympathetic dystrophies. As in rheumatoid arthritis, the pathogenesis of the reflex sympathetic dystrophies is poorly understood,[11] but it is apparent that sympathectomy and sympathetic blocking agents, such as tetraethylammonium chloride[9] and hexamethonium compounds,[10] are effective in their treatment.

Hexamethonium chloride (Methium*) was used in our series of patients with rheumatoid arthritis. Trevor H. Howell[12] used tetraethylammonium bromide in a series of 26 patients and demonstrated temporary improvement of pain with successive injections. All but seven of his patients showed some degree of improvement. The use of hexamethonium chloride seems desirable because of its ease of administration orally and because of its greater potency as compared to tetraethylammonium bromide.

Method of Study

Sixteen patients with arthritis were given hexamethonium chloride over a period of from two to nine months. We treated nine patients with pure rheumatoid arthritis, three with known osteoarthritis but with definite active rheumatoid arthritis in addition, three with rheumatoid spondylitis (Marie-Strümpell), and two with pure osteoarthritis. One patient had rheumatoid arthritis of the peripheral joints as well as spondylitis. Of the 12 patients with rheumatoid arthritis of their peripheral joints, nine were women and three were men. The average age of this group was 48 years. Each patient with rheumatoid arthritis was classified according to the outline recommended by the American Rheumatism Association.[14] Since most of our patients were ambulatory, they fell into the less advanced stages of rheumatoid progression (table 1).

Each patient was studied by measuring joint circumferences and range of motion in order to detect decreased swelling or increased motility as a result of therapy. Laboratory studies, including erythrocyte sedimentation rates, hematocrits and hemoglobin determinations, were followed regularly. Changes in appetite and weight were noted, as well as symptomatic changes related to the joints involved. All patients were in an active stage of their disease, complaining of pain at the time treatment was instituted. The sequence of treatment consisted of starting the patient on hexamethonium chloride for a period of observation and then stopping therapy long enough to note a recurrence of symptoms. We resumed treatment after symptoms reappeared to observe a second response and confirm the levels of the minimal effective dose, the optimal dose, and the maximal tolerated dose in each patient. In many patients we were able to observe a separate response to

*Methium (brand of hexamethonium chloride), supplied by Warner-Chilcott Laboratories, New York.

TABLE 1
Classification of Rheumatoid Progression

Stage	Roentgenologic Signs	Muscle Atrophy	Extra-Articular Lesions (Nodules; Tenovaginitis)	Joint Deformity	Ankylosis
I	Osteoporosis (sometimes no destructive changes)	0	0	0	0
II	Osteoporosis (sl. cartilage or subchondral bone destruction may be present)	Adjacent	May be present	0	0
III	Osteoporosis (cartilage destruction, bone destruction)	Extensive	May be present	Subluxation, ulnar deviation and/or hyper-extension	0
IV	Same as III with bony ankylosis	Extensive	May be present	Same as III	Fibrous or bony ankylosis

therapy three times. We did not employ the double-blindfold method with placebos, because the real medication is so readily identified by its side effects.

Dose and Administration

The administration of hexamethonium chloride was handled with the same caution as that prescribed for its use in hypertension.[15] We began treatment by giving one 125 mg. tablet on the first day, followed by daily increases of 125 mg. At the end of eight days the patient had reached a dose of 250 mg. four times daily. In most of our patients with a good response, a slight effect was noted on reaching 125 mg. four times daily. However, when the dose was increased the beneficial effect was proportionately greater. After reaching a dose of 250 mg. four times daily we increased the intake by 125 mg. every two days until intolerance to the medication was demonstrated or until maximal benefit was obtained. In most cases a dose of 375 to 500 mg. four times daily was found to be optimal, although a few obtained satisfactory relief from 250 mg. four times daily. The incidence of side effects was greater at the level of 500 mg. four times daily, yet those patients who obtained relief at this level preferred to put up with minor side effects rather than sacrifice the benefits of the medication.

Toxicity of Hexamethonium Chloride

The dosage of hexamethonium was largely determined by the tolerance of the individual to this medication. The factor of intolerance demands close attention, since the side effects are many and sometimes dangerous. The

sequence of severe constipation and increased absorption of hexamethonium salts, cited by Klayman et al.,[13] produced paralytic ileus in one of our patients. This complication can be avoided by urging patients to be sure to have a daily bowel movement. If the patient is unable to evacuate for 48 hours he should be advised to discontinue the medication. Other symptoms, such as lightheadedness, fainting, change in libido, urinary retention, visual disturbances and nausea, can be minimized by careful administration. Eleven out of 16 patients noticed one or more side effects (table 2).

We performed urine concentration and blood nonprotein nitrogen tests on all patients before starting treatment so as to foresee the possibility of

TABLE 2

Side Effects of Hexamethonium Chloride in 16 Patients

Symptom	No. of Pts.
Constipation	7
Fainting	0
Urinary retention	1
Visual blurring	4
Nausea	5
Decrease in libido	0
Lightheadedness	6

toxicity due to increased retention. We observed that patients under 50 years of age tolerated their medication better than those over 50, possibly because of better bowel action and renal function.

RESULTS

Nine patients with pure rheumatoid arthritis were treated during a period of pain. Varying degrees of swelling, redness, and subjective and objective stiffness were present. We attempted to differentiate between the pain caused by activity such as weight-bearing and that present when the patient was at rest. The latter is a more dependable symptom in which to recognize change, since it does not become confused with stiffness of the joints and muscle soreness due to activity.

Table 3 shows that eight of our patients (88%) with pure rheumatoid arthritis had some degree of improvement of their pain. Seven (78%) had complete relief while at rest, and five (55%) had from very marked to complete relief while active. Those in the early stages of rheumatoid progression were benefited most by the treatment, as four out of five with very marked to complete improvement while at rest and in motion were in stages I or II of rheumatoid progression. Where ankylosis and joint destruction had taken place in specific joints and in individual patients, the improvement was slight or moderate. For example, one patient had grade III changes in her hands and knees and grade I changes in her elbows, hips and costosternal joints. The pain in the latter three joints cleared completely in therapy, whereas the knees and hands improved only slightly. These findings are in conformity with those of Rowntree et al.[1] following sympathectomy.

It was apparent that joint swelling subsided to a less marked degree than did pain, although in some cases the results were striking. We observed that five patients (55%) had some degree of improvement of this sign. Stiffness and limited joint motion in patients with grades I and II progression improved to a degree equal to the improvement of pain. However, the patients with deformed joints of far advanced disease did not enjoy so much improvement in joint flexibility.

Seven patients (78%) had an improvement in their functional capacities (table 4) and were able to be placed in a less limited functional classification during treatment. Two patients moved from Class 2 to Class 1, two patients moved from Class 3 to Classes 1 and 2, and three patients moved from Class 4 to Classes 2 and 3.

In six patients, coldness, numbness, unusual sweating or tingling was noted before treatment. These symptoms were decreased during treatment

TABLE 3

Effect of Hexamethonium Chloride on Symptoms and Signs of Rheumatoid Arthritis

	Stage of Rheumatoid Progression	Patient	Degree of Improvement			
			Pain		Swelling	Motion
			While Active	At Rest		
9 patients with pure rheumatoid arthritis	I	1	5+	5+	3+	****
		2	4+	5+	***	4+
		3	4+	5+	4+	4+
	II	4	4+	5+	5+	4+
	III	5	4+	5+	2+	4+
		6	1+	5+	0	2+
		7	2+	5+	1+	1+
		8	0	0	0	0
	IV	9	1+	**	0	0
3 patients with active rheumatoid arthritis plus hypertrophic arthritis	I	1	3+	**	0	3+
	II	2	3+	5+	2+	3+
	III	3	3+	4+	2+	3+
3 patients with rheumatoid spondylitis	III	1	0	0		0
		2	0	0		0
		3	0	0		0

5+ Complete.
4+ Very marked.
3+ Marked.
2+ Moderate.
1+ Slight.
0 None.
** No pain at rest at start of treatment.
*** No swelling at start of treatment.
**** No limitation of motion at start of treatment.

TABLE 4

Classification of Functional Capacity

Class	
I	Complete ability to carry on all usual duties without handicaps
II	Adequate for normal activities despite handicap of discomfort or limited motion at one or more joints
III	Limited only to little or none of duties of usual occupation or self-care
IV	Incapacitated, largely or wholly bedridden or confined to wheelchair; little or no self-care

in five. The effects on weight, appetite and hematocrit were not consistent enough to report.

On several trial courses of hexamethonium chloride the response of each patient was similar to that observed in the initial course of treatment. The minimal effective dose, optimal dose, maximal tolerated dose and clinical response to therapy were similar enough in each individual to denote consistency. In the nine patients with pure rheumatoid arthritis, we were able to observe 21 different courses of therapy.

The duration of maximal benefit from each dose varied somewhat in individuals but was found to be, roughly, three hours. Most patients felt a temporary symptomatic improvement with each dose as well as a gradual amelioration of symptoms during the course of treatment. The patients who experienced their worst symptoms in the morning on rising preferred to take their first dose at 4:00 a.m. before rising.

The lag in reappearance of symptoms after cessation of therapy varied greatly, as one would expect. The normal pattern of rheumatoid arthritis is one of fluctuation. Those with the more rapid sedimentation rates and more advanced progression seemed to flare up within one or three days after the medication was stopped. Others with less active disease remained in remission for as long as six weeks. In no case was a marked flare-up noticed in less than 24 hours after cessation of therapy, probably because of delayed absorption of hexamethonium chloride.[13]

The patients were questioned regarding the comparative effects of hexamethonium chloride and salicylates used previously. All but one of those who benefited by hexamethonium therapy felt that it was definitely superior. In cases where the symptoms of rheumatoid arthritis were improved only partially by the use of hexamethonium, we allowed the use of salicylates in addition to hexamethonium chloride, with increased benefit regarding pain. This was done only after the effect of hexamethonium had been established.

We observed no consistent changes in the erythrocyte sedimentation rates which would indicate that rheumatoid activity was affected by hexamethonium. We also noted flare-ups of rheumatoid activity during treatment. However, the patients felt that their symptoms were of shorter duration and of less degree than before treatment. This impression was substantiated by the withdrawal of therapy during these flare-ups and the finding of a definite increase in pain.

The one patient who had no response to hexamethonium had been taking cortisone in maintenance doses up to three weeks before hexamethonium was started. She was having very marked pain in all her peripheral joints at the time therapy was initiated, and tolerated the average optimal dose of 500 mg. four times daily for one week. At this time, she refused further medication because of lack of benefit. The only other patient who had been on cortisone immediately before starting hexamethonium received complete relief of pain in all joints while at rest, very marked benefit in her knees and ankles while active, and moderate improvement in her hands, elbows and shoulders. However, we noted that this patient had no improvement until a dose of 350 mg. four times daily had been reached, a higher dose than the average patient required for initial benefit. No definite conclusions can be drawn from the experience with these two patients, but the findings would suggest that the exacerbation following withdrawal of steroid therapy is more resistant to hexamethonium therapy than the usual rheumatoid exacerbation.

Three patients with x-ray evidence of mild hypertrophic arthritis but with definite rheumatoid changes and elevated erythrocyte sedimentation rates were treated with a satisfactory response. These patients were chosen because the clinical diagnosis in each had been rheumatoid arthritis with an incidental finding of hypertrophic lipping by x-ray examination. Two had from very marked to complete relief of pain while at rest, and all three had marked improvement while active (table 3). In these three patients we observed seven separate courses of therapy with consistent responses. Two patients with clinical and x-ray evidence of pure hypertrophic arthritis had no response to hexamethonium chloride.

Three patients with rheumatoid spondylitis, one of whom was included in the group with rheumatoid arthritis of the peripheral joints, were treated without evidence of improvement (table 3). The one patient who had both conditions responded with a very marked improvement of his peripheral joints but not of his spinal symptoms.

Discussion

The nerve supply of the synovial membranes is primarily of sympathetic origin.[11] It can be assumed that these fibers carry primarily efferent impulses. This is suggested by the fact that the synovial membranes are relatively insensitive structures and are probably not responsible for much of the pain sensation experienced in joint disease.[18] The fibrous joint capsule, on the other hand, is a very sensitive structure and contains many nerve endings of obscure origin, most of which are probably somatic. If we accept the thesis that there may be a similar basis for the production of signs and symptoms in rheumatoid arthritis and the reflex sympathetic dystrophies, we can postulate that an inciting pain focus lies in the joint capsule, probably as a result of inflammation. The continuous bombard-

ment of painful stimuli from the capsule would set up a diffuse reaction via the internuncial pool through a variety of motor nerves, primarily autonomic, causing vegetative disturbances in the involved extremity. Through some means as yet unexplained, a self-perpetuating reflex is set up by the return impulses through the efferent autonomics to the original site of pain production, the capsule. If this chain were broken by interruption of the sympathetic nerve pathways, the pain and vegetative disturbances would presumably cease. This, of course, is a description of the working hypothesis used to explain the reflex sympathetic dystrophies and their response to hexamethonium salts.[17] It can be applied to rheumatoid arthritis also. We note that the symptoms of reflex sympathetic dystrophies are helped only during the time that hexamethonium salts are being administered.[10] The flare-up following cessation of therapy would indicate that the original pain focus still existed. In our series, we noted no change in the inflammatory reaction of rheumatoid arthritis as measured by the erythrocyte sedimentation rates, and we found that the original symptoms recurred after cessation of therapy. For this reason, we propose that hexamethonium did not influence the inflammatory aspect of rheumatoid arthritis in any way, but did produce an amelioration of symptoms through the mechanism described above.

A relationship between the shoulder-hand syndrome and rheumatoid arthritis is suggested by a patient under our care, but not included in this series, who developed the typical pattern of shoulder-hand syndrome following a hemiplegia, which later progressed to a typical picture of rheumatoid arthritis involving all the peripheral joints. We might also note, in reference to the inflammatory focus mentioned above as the initiating force in the self-perpetuating pain cycle, that focal abscesses far from the joints can initiate a disease of the joints resembling rheumatoid arthritis.

The effect of tetraethylammonium bromide on rheumatoid arthritis described by Howell [12] has been ascribed to an analgesic action.[14] However, the lack of effectiveness of hexamethonium in our two patients with pure hypertrophic arthritis and three patients with rheumatoid spondylitis suggests a more selective action than a pure analgesic might have. Although an ordinary analgesic might improve subjective stiffness and limitation of joint motion by reduction of pain, swelling would not be likely to be reduced. Since swelling was reduced in seven out of 12 cases in our series, we cannot attribute the effect of hexamethonium chloride to analgesia alone.

The increased skin temperature and blood flow of the extremities known to occur with hexamethonium therapy [16] cannot be disregarded as a factor in producing amelioration of joint pain. The reported failures in the use of other vasodilators do not indicate that this medication does not effect its benefit by its very potent vasodilatory action. It may be simply a matter of degree.

Recently it has been observed [19] that certain hypertensive patients on hexamethonium chloride and Apresoline therapy have developed rheumatoid

arthritis while under treatment. The incidence of this unusual complication is high enough to incriminate the hypotensive agents used. This observation is certainly in direct contradiction to the results reported here using hexamethonium chloride, and we cannot explain this discrepancy. However, in no case treated in this series did we notice an increase in symptoms.

The evidence presented here of improvement of joint symptoms with hexamethonium cannot be interpreted as conclusive. The natural exacerbations and remissions of the disease make it difficult to evaluate the response to treatment in so short a series. However, the results are encouraging enough to warrant further trial.

Summary

1. Nine patients with pure rheumatoid arthritis and three patients with rheumatoid arthritis plus hypertrophic arthritis were treated with hexamethonium chloride over a period of two to nine months. Twenty-eight responses to therapy were observed.

2. Three patients with rheumatoid spondylitis and two patients with pure hypertrophic arthritis were similarly treated.

3. The therapy was considered to cause a symptomatic improvement in rheumatoid arthritis without altering the course of the disease.

4. The results of therapy were encouraging enough to warrant further trial.

5. A theory is proposed which compares rheumatoid arthritis and the reflex sympathetic dystrophies and offers a possible explanation of the response to hexamethonium therapy in rheumatoid arthritis.

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SOME OBSERVATIONS ON TELESCOPED URINARY SEDIMENTS *

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STUDY of the kidney lesions of periarteritis nodosa has been carried on since the first comprehensive description of the disease in 1866.[1] Renal involvement has been estimated to be as high as 87%. Many excellent reviews of the renal pathology of periarteritis have been published, and several classifications of the type and degree of renal involvement are available.[2-6]

Similarly, a great volume of published material has considered the high incidence of renal lesions associated with disseminated lupus erythematosus.[7-14] Despite this vast literature, relatively little attention has been paid to the clinical urinary findings in these diseases. A disregard of this readily available diagnostic aid may well have contributed to the strikingly low antemortem diagnosis rate noted by several authors.[15]

Krupp in 1943 [16] focused attention on this group of diseases by describing a type of urinary sediment believed to be characteristic of periarteritis and lupus erythematosus. He combined these diseases under the term "visceral angiitis," and noted the presence of red cells, red cell casts, oval fat bodies, fatty and waxy casts and broad casts in the same urine specimen together with an abnormal amount of protein. This combination has been described as a telescoped urinary sediment and is illustrated in figure 1. Addis [16-17] is quoted as never having seen this type of sediment in chronic glomerulonephritis. Reports confirmatory of Krupp's observations have been published by Miale [18] and Cole,[19] and the finding has been widely accepted in clinical laboratories as being characteristic if not pathognomonic of "visceral angiitis."

It would be possible on an entirely theoretical basis to construct a case of chronic glomerulonephritis which might indeed demonstrate all the features of this telescoped urinary sediment. Such a patient would have suffered from chronic glomerulonephritis for many years in order to produce an advanced deterioration of renal function and the dilated tubules required for the production of broad renal failure casts. Late in the course of his disease a nephrotic syndrome would have supervened in order to provide a massive albuminuria and the presence of large amounts of fat bodies, epithelial cells and double refractile fat bodies. An acute exacerbation of glomerulonephritis might signal remission of the nephrotic syndrome and provide the inflammatory elements of red blood cells and red cell casts to complete the telescoped sediment. In our experience this precise sequence

* Received for publication July 3, 1954.

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of events is not at all unusual in the natural history of chronic glomerulonephritis, in contrast to the published observations of other authors.

With this conflict in mind, urinary sediments were carefully scrutinized from patients suspected of chronic glomerulonephritis who were admitted to the Georgetown University Hospital during 1953. This survey yielded three patients with a clinical picture either typical or highly suggestive of chronic glomerulonephritis with negative studies for lupus erythematosus and periarteritis nodosa. They demonstrated a typical telescoped sediment, they died with a clinical diagnosis of chronic glomerulonephritis, and at autopsy they showed histologic evidence of chronic glomerulonephritis without evidence of any visceral angiitis present in other organs. In addition,

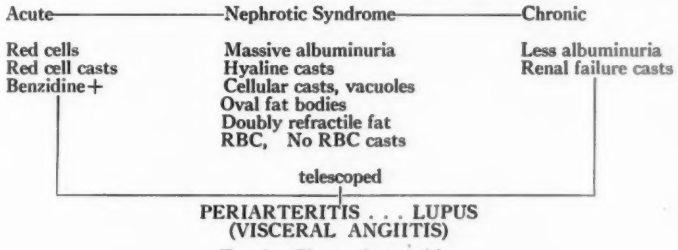

FIG. 1. Glomerulonephritis.

we have seen a telescoped sediment in a patient diagnosed clinically as subacute bacterial endocarditis. Since this patient is still living he is not included in the present report, which is confined to pathologically proved cases.

CASE REPORTS

Case 1. A 49 year old white female was admitted for renal evaluation.

Present Illness: At age 20, during her only pregnancy, she was found to have definite albuminuria, hypertension and edema of the legs without renal infection. Delivery of a normal child was precipitated. Albuminuria continued during the postpartum period and she was kept on digitalis for several years. There were no major complaints until age 42, when she noted the insidious onset of fatigue, dyspnea on exertion, orthopnea, anterior chest pain associated with exertion and/or excitement, and progressively increasing ankle edema. She had noted several episodes of paroxysmal nocturnal dyspnea. She was found to have hypertension, microscopic hematuria, cardiac enlargement and a systolic murmur. A diagnosis of collagen disease was entertained. The final impression was rheumatic fever, and she was placed on bed-rest and salicylates for nine months. She was much improved for the succeeding four years except for occasional dyspnea on exertion, paroxysmal nocturnal dyspnea, night sweats and chest pains. However, two years previous to this admission there was a gradual return of leg edema. Three crops of painful pustules appeared on her face and left arm. These were treated with antibiotics. Ten months previous to admission she noted the first periorbital edema on awakening in the morning. Since then there has been relentless progression of easy fatigability, drowsiness, decreasing exercise tolerance, shortness of breath on exertion, tinnitus and occipital headache. Two months previous to admission there was sudden development of massive peripheral edema and ascites, with a weight gain of 15 pounds.

She was treated with mercurial injections, which produced a 12 pound weight loss and the development of profound nausea and vomiting. Thereafter she developed blurring and marked diminution of visual acuity, inability to focus on close objects, and continuous nausea and vomiting every morning, which she likened to the hyperemesis of pregnancy.

System review and family history were noncontributory except that the patient had noted frequent sore throats during her early life, with an average of several upper respiratory infections a year. A tonsillectomy had been performed at the age of 43.

Physical Examination: Pulse, 96; respirations, 21; temperature, 98° F.; average blood pressure, 230/130 mm. of Hg. The patient was a well developed, somewhat thin white female in no acute distress. Funduscopic examination revealed bilateral papilledema, fresh and old hemorrhages both deep and superficial, large, fluffy exudates concentrated around the macula to form a classic macular star, arteriovenous compression, irregularity, thickening and beading of arterioles and moderate retinal edema. The fundi were interpreted as grade IV Keith-Wagner. The chest showed moist râles in both bases posteriorly. The heart was enlarged to percussion and auscultation. Ventricular rate was 96, with a normal sinus rhythm. A grade III apical systolic and a grade II aortic blowing systolic murmur were heard. The liver was felt 2 cm. below the costal margin. Shifting dullness was present. Extremities showed 2 plus pitting edema, and freely movable ankle and pedal edema. There was also sacral edema and edema of the lower abdominal wall.

Laboratory Work: Specific gravities were fixed at 1.010 or below; pH, 5.5; albumin, 4 plus. Urinary sediments revealed more than 100 red blood cells per high power field, 10 to 12 waxy casts, 3 to 5 granular casts, 6 to 8 blood casts, broad renal failure casts, and white cells. The patient was anemic, with a hemoglobin of 9 gm. and a hematocrit of 38%. Corrected sedimentation rate was 24 mm. per hour; white count, 16,000, with 16% myelocytes, 5% monocytes, 1% eosinophils, 60% polymorphonuclear cells, 18% band forms. Total eosinophil count was 180; icteric index, 5; urea nitrogen, 46; creatinine, 5.7; cholesterol, 520 mg. %. CO_2 combining power was 14 mm./L.; chlorides, 96; potassium, 4.7; sodium, 124; phosphorus, 10 mg. %; total protein, 4.6 gm. %; albumin, 1.9; globulin, 2.7. VDRL was negative, two preparations for L.E. cells were negative, and stools were guaiac negative. The chest roentgenogram revealed a moderate amount of fluid in the left pleural cavity, an enlarged heart and increased vascular markings. Electrocardiogram revealed no deviation of the electrical axis, normal sinus rhythm, and no abnormalities in T-waves or ST segment.

Hospital Course: The patient had several episodes of severe oliguria and occasional anuria, sometimes lasting as long as four or five days. Uremic gastritis represented a major management problem and failed to respond to any treatment except the use of Thorazine.* There were two episodes of acute pulmonary edema which required full emergency therapy. The patient's weight gradually fell from 115 to 108 pounds. Azotemia gradually increased, reaching a blood urea nitrogen of 110 mg. % and creatinine of 13.5. Hypertension was maintained throughout the hospital course, but was reduced somewhat with improved fluid and electrolyte management; it averaged 190/90 mm. of Hg during the last several weeks of hospitalization.

Several urines examined in the renal laboratory revealed a true telescoped sediment with massive albuminuria (8.4 gm. per 24 hours), red blood cells, typical red blood cell casts (illustrated in figure 2), granular casts, hyaline casts, white blood cells, broad renal failure casts, and numerous doubly refractile fat bodies on examination through the polarizing microscope.[20]

Nausea, vomiting, retching and tissue wasting were progressive. On the forty-

* Supplied by Smith, Kline, and French Laboratories.

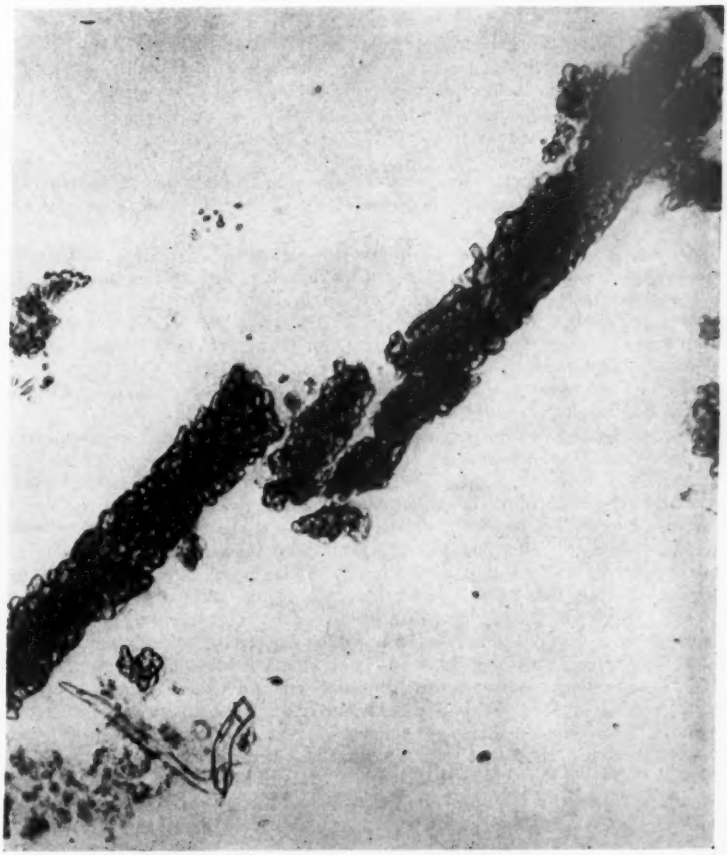

FIG. 2. Red blood cell cast and red cells in unstained fresh urine of a patient with telescoped urinary sediment (44×).

eighth hospital day a pericardial friction rub was noted that increased in severity. Increasing drowsiness and mental changes were noted. A frank toxic psychosis developed on the fifty-sixth hospital day. She also developed involuntary twitchings of the hands and feet and a positive Chvostek's sign. The urine output continued to diminish progressively, and her total output in the last 10 days of hospitalization was 465 c.c. Retinal changes progressed to the point of complete blindness, and the patient died on the fifty-ninth hospital day.

Clinical Diagnoses:

1. Chronic glomerulonephritis, including nephrotic syndrome and acute exacerbation of glomerulonephritis.
2. Hypertensive heart disease and congestive failure.
3. Uremic syndrome and terminal toxic psychosis and coma.

Pathologic Diagnoses:

1. General: Anasarca, pleural effusion, pericardial effusion, ascites.
2. Lungs: Pulmonary congestion, edema, interstitial pneumonitis.
3. Cardiovascular: Acute fibrinous pericarditis, cardiac hypertrophy, interstitial myocarditis, mitral valvular fibrosis, arteriosclerosis of the aorta, generalized arteriosclerosis.
4. Liver and spleen: Chronic passive congestion.
5. Genitourinary tract: Chronic glomerulonephritis with marked acute exacerbation. Arterionephrosclerosis, fibromyoma of the uterus, chronic cystic cervicitis.

Description of the Kidney: The kidneys weighed approximately 120 gm. The cortex was thin, with many scars. Section revealed a thickened capsule with a collection of round cells. The glomeruli showed scarring and proliferation of Bowman's capsule, forming typical epithelial crescents. The vessels show endothelial proliferation and thickening. There was an increase in fibrous stroma between the tubules. Changes are illustrated in figure 3a.

Case 2. A 50 year old white female was admitted to the hospital with the chief complaints of respiratory infection, fever and cough.

Present Illness: Twenty years previous to admission she had sustained fracture of the spine resulting in temporary paralysis and anesthesia of the lower extremities, with inability to void or defecate. There was one report of albuminuria. Four years previous to her admission the albuminuria was definitely established during admission for elective surgery. One year previous to admission she had had frequent syncopal attacks, followed by severe headaches, vertigo and blurring of vision. She had a blood pressure of 230/130 mm. of Hg and was diagnosed as essential hypertension. This time she was also noted to have severe bronchial asthma and a urinary tract infection. Albuminuria continued and seemed to be more severe. She then developed edema of the eyelids rather suddenly, which disappeared quickly with a 25 pound weight loss. Eleven months previous to admission she was admitted to another hospital with a diagnosis of hypertension, hypertensive heart disease and acute pyelonephritis. During this admission she developed chest pain and pleural effusion, and was thought to have a pulmonary embolus. Eight months previously she had developed anorexia, nausea, vomiting, dizzy spells, burning on urination, and nocturia. No edema was noted, but she had a grade III Keith-Wagner retinopathy, hepatomegaly, cardiomegaly, with an auricular gallop, and a blood pressure of 210/113 mm. of Hg. The albuminuria was persistent. She was treated with hexamethonium and her blood pressure dropped to average levels of 180/110 mm. of Hg. A final diagnosis of chronic pyelonephritis, hypertension and hypertensive heart disease was made. In the six months preceding the current admission she was hospitalized four times for management of her hypertensive heart disease. Dyspnea was the chief complaint on most of these admissions.

Physical examination revealed a well developed, well nourished white female with wheezing and dyspnea. Temperature was 99.2° F.; respirations, 30; pulse rate, 90 per minute; blood pressure, 200/110 mm. of Hg. Funduscopic examination revealed grade IV Keith-Wagner eyegrounds, with some blurring of the disc margins, narrowing, beading, tortuosity of the arterioles, and increased light reflex. One fresh hemorrhage and many old exudates were present, most of them clustered around the macula in the distribution of a typical macular star. The lungs showed numerous expiratory wheezes, and rhonchi with a few moist râles posteriorly at the bases. Her heart was enlarged and had a normal sinus rhythm, with a grade II systolic murmur at the apex. The pulmonic second sound was louder than the aortic second sound. The abdomen had a positive fluid wave. No organs were palpable, but she had some tenderness on deep palpation over the left kidney. Extremities showed 3

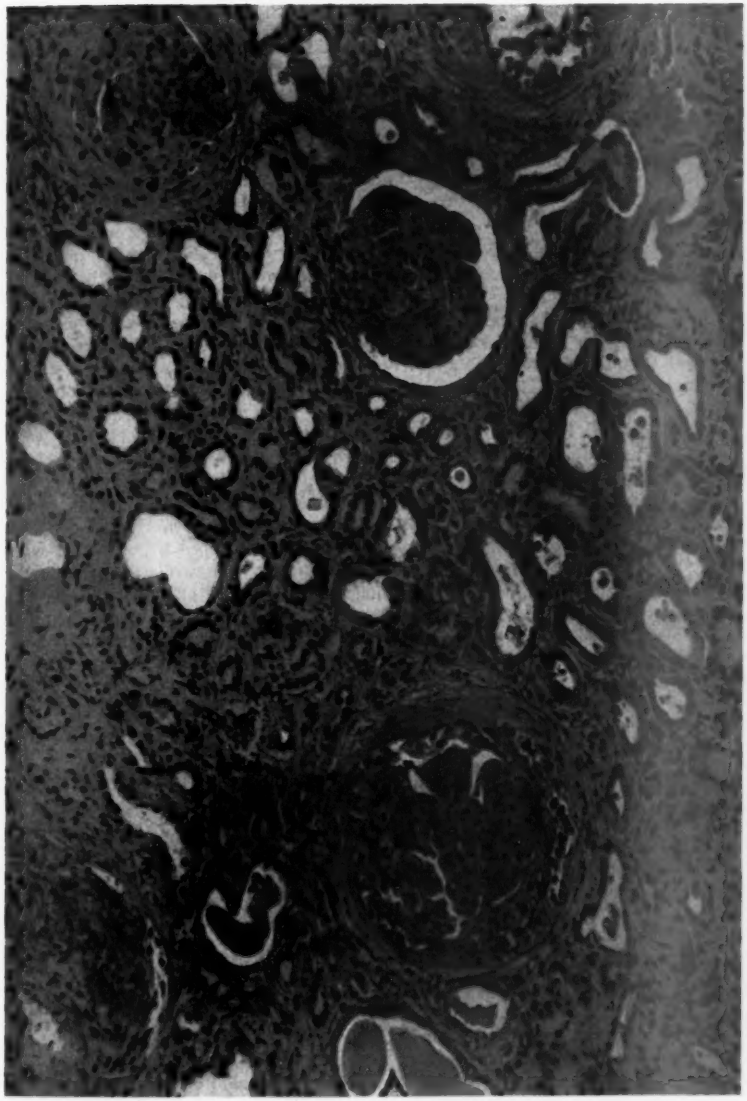

FIG. 3A. Photomicrograph (78×) of a section through the renal cortex of case 1. Note thickened Bowman's capsule, crescent formation and fibrosis of glomeruli.

plus pitting edema of the legs and ankles, together with sacral edema and edema of the forearms. The skin seemed tight and full over all extremities.

Laboratory Findings: Quantitative urinary sediment revealed a specific gravity of 1.014; 2.74 gm. protein; 45,000,000 red cells, 120,000,000 white cells, 300,000 casts per 24 hours. Examination of the fresh sediment revealed numerous red cells, classic red blood cell casts, granular casts, hyaline casts, broad renal failure casts, and numerous doubly refractile fat bodies comprising a characteristic telescoped sediment. She had a sodium of 138, potassium of 5, and a chloride of 111 mEq./L. Blood urea nitrogen was 77; creatinine, 11.5 mg. %; total protein, 5.1; albumin, 2.7; globulin, 2.4 %. She was anemic, with a hematocrit of 26; the sedimentation rate was 14 mm. per hour; white count, 7,200, with 1% eosinophils, 16% lymphs, and 83% mature polymorphonuclear cells. Total eosinophil count was 12; icterus index was 5. Serology, guaiac examination of the stool and search for L.E. cells were all negative. Coagulation time was 11 minutes. Urine culture showed a few colonies of paracolon and *Escherichia coli.* Subsequent urine cultures grew out *B. proteus* in addition. X-ray of the chest showed emphysematous lung structure, accentuation of vascular markings, a triangular area of increased density in the right lower lobe (thought to represent pneumonic infiltration), and irregularity in the region of the left costophrenic angle due to fluid. The heart was enlarged and the aorta was tortuous and elongated.

Hospital Course: Patient continued to have profuse albuminuria, and there were findings of a telescoped urinary sediment. On repeated examinations the blood cholesterol was elevated to 340 mg.%. Urine output remained very low from the day of admission and averaged 250 c.c. per day during the first week and 125 c.c. per day during the second week. The patient became progressively more confused and more azotemic, and on the fourteenth hospital day she developed a pericardial friction rub. She also developed severe pain, chills, fever, tachycardia, disorientation, and tenderness localized in the left lower quadrant. Physical examination revealed true rebound tenderness over that area. Diminution in peristaltic sounds suggested a localized peritonitis. She also developed a severe parotitis after the administration of potassium iodide. Her clinical condition rapidly deteriorated, with the development of clonus, trismus of the jaw, pallor of the mucous membranes, continued disorientation and, finally, coma. She died on the seventeenth hospital day.

Clinical Diagnoses:

1. Chronic glomerulonephritis, with nephrotic syndrome and acute exacerbation of glomerulonephritis occurring in the terminal phase of her disease.
2. Chronic pyelonephritis superimposed on the above.
3. Hypertension, hypertensive heart disease.
4. Chronic asthmatic bronchitis.
5. Localized peritonitis due to penetrating renal abscess.

Pathologic Diagnoses:

1. Lungs: Pulmonary emphysema; chronic vascular congestion; focal atelectasis; bronchial asthma with hyaline membranes.
2. Cardiovascular: Pericarditis (serofibrinous); hypertrophy of the myocardium, most marked in the left ventricle; arteriosclerosis.
3. Gastrointestinal: Chronic passive congestion of the liver; hepatic edema.
4. Genitourinary: Chronic glomerulonephritis (bilateral); chronic pyelonephritis (bilateral).

Description of the Kidney: The kidneys weighed 130 and 140 gm. and had a contracted appearance. Capsule was thickened and edematous. Surfaces were granular and showed multiple stellate scars. Sections from both kidneys showed changes char-

acteristic of both chronic glomerulonephritis and associated pyelonephritis. The majority of the glomeruli were partially or completely changed into hyaline masses or reduced to small fibrous masses. Some were enlarged and lobulated. Others showed epithelial crescents or foci of hyaline necrosis, adhesions of the glomerular tuft to the capsule or crescent, and early fibroplastic proliferation of some of the tufts. There was a marked interstitial cellular infiltration, interstitial fibrosis and marked enlargement of the tubules. The dilated tubules were filled with hyaline or colloid casts. The blood vessels were markedly thickened, demonstrating chronic obliterative changes with fibrosis of the medial coat. These microscopic changes are illustrated in figure 3b.

Case 3. A 61 year old white male was admitted to the hospital with epigastric pain.

Present Illness: Seven months previous to admission he had been discharged from the hospital with a diagnosis of duodenal ulcer based on the demonstration of a deformity of the duodenal cap and ulcer niche in the duodenum. At that time he had persistent albuminuria. The urine sediment showed a microscopic hematuria, with 2 to 15 red cells per high power field and 2–30 white cells per high power field, with occasional granular casts. Specific gravity ranged from 1.004 to 1.012, pH from 5 to 6.5. He was moderately anemic, with a hemoglobin of 9.5 gm. and a hematocrit of 31. Sedimentation rate was elevated at 31 mm. per hour (corrected); white count and differential were normal; total eosinophil count was 110. Phenolsulfonphthalein excretion totaled 15% in two hours. Urine culture was positive for *Staphylococcus aureus.* X-ray of the abdomen showed two small areas of calcification projected into the right kidney suggestive of small calculi. The limitation of renal function did not permit good visualization on the intravenous pyelogram. He was discharged from the hospital with a diagnosis of chronic pyelonephritis and duodenal ulcer, and was followed in the clinic until a recurrence of epigastric pain precipitated the admission to surgical service for consideration of gastric surgery. The pain was high in the epigastrium, sharp and constant, and was relieved by injection of analgesics. The patient also complained of cramping pains in both legs, usually more severe in one leg at a time and generally confined to the thigh. He also noted weight loss, difficulty in starting urination, and occasional dysuria and nocturia. Gastrointestinal x-ray revealed a large ulcer niche visualized in the lesser curvature of the stomach, and examination of the stools was positive for free blood. The patient was being prepared for surgery when reëvaluation by the renal service revealed the following: extreme weakness, easy fatigability and a 30 pound weight loss, together with an active gastric ulcer and gastrointestinal bleeding.

Physical Examination: Temperature, 98.6° F.; pulse, 80; respirations, 20; blood pressure, 170/100 mm. of Hg. Vitiligo and pallor were noted on the face. Funduscopic examination revealed increased light reflex, narrowing and tortuosity of the arterioles, and arteriovenous compression interpreted as grade II.

Laboratory: Urinalysis showed a specific gravity of 1.012 or less; pH, 7.5; albumin, 4 plus; 15 to 20 white cells per high power field, of which 40% were positive with Sternheimer-Malbin motility cell stain. There were 50 to 200 red cells, 1 to 2 hyaline casts, 2 to 4 granular casts, broad renal failure casts, occasional blood casts, and many doubly refractile-fat bodies comprising a telescoped sediment. Quantitative albumin was 20 gm. per 24 hours. Quantitative sediment by the Addis technic revealed a specific gravity of 1.010, 630,000 casts, two billion red cells, and 19,000,000 white and epithelial cells in 24 hours. Total eosinophil count was 1,500 per cubic millimeter. Phenosulfonphthalein excretion showed only a trace in two hours. Blood urea nitrogen was 128 mg.%, creatinine, 11.7 mg.%; phosphorus, 7.6 mg.%; sodium, 132; chloride, 103; potassium, 6.7 mEq./L.

Hospital Course: The finding of a telescoped urinary sediment, together with eosinophilia, brought up the distinct possibility of a collagen disease such as peri-

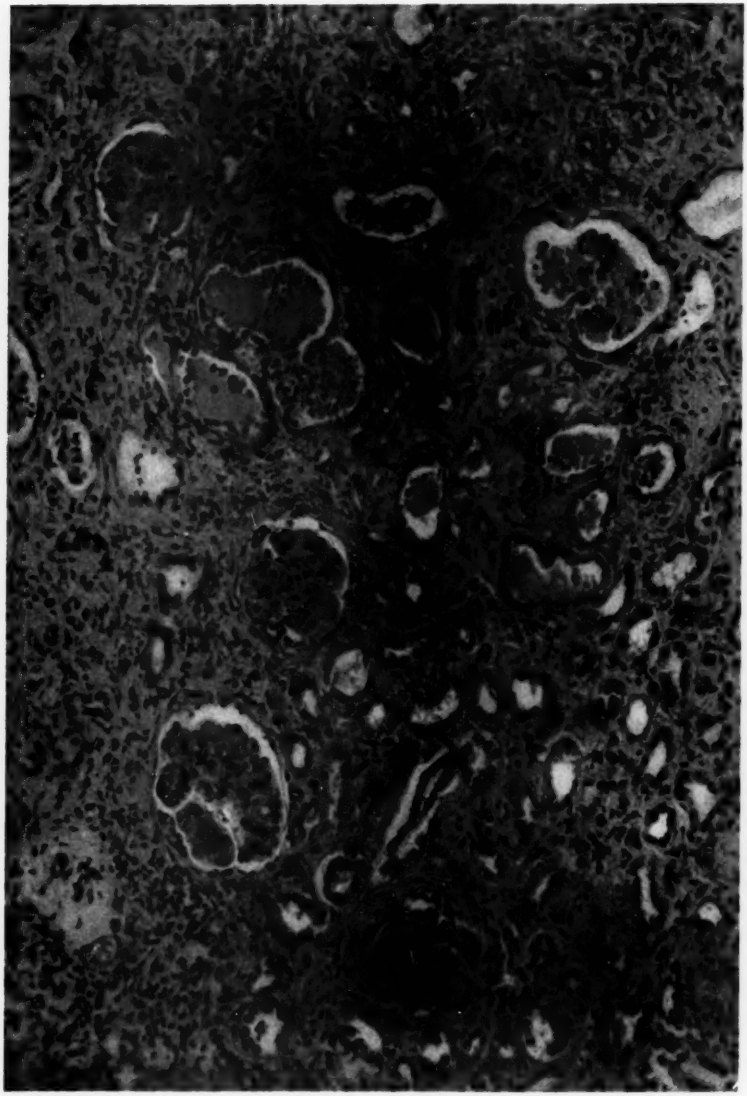

FIG. 3B. Photomicrograph (78 ×) of renal cortex of case 2. In addition to the primary glomerular disease, there are obliterative changes in blood vessels.

arteritis or lupus erythematosus. The muscle pains, the gastric ulcer and the hypertension strengthened the clinical diagnosis of periarteritis nodosa. Several searches for lupus erythematosus cells were negative. Two biopsies taken of the left gastrocnemius and left thigh revealed thick walled blood vessels showing hyalinization with no evidence of inflammatory reaction. The patient continued to have recurrent abdominal and muscle pains in the absence of any fever. He had a relentlessly progressive renal insufficiency, with gradually increasing azotemia and progressive development of oliguria. A telescopic urine was repeatedly demonstrated. On one or two occasions he developed gross, painless hematuria. Hypertension continued to be of moderate severity. In the course of his illness he developed left knee, hip and shoulder joint pain and aches, and a generalized papular urticaria. He was given conservative therapy for his uremia, with dietary management and correction of electrolyte imbalances as they occurred. He remained in a fairly comfortable state, with a gradual downward course, until he passed into uremic coma and died on the fifty-fifth hospital day.

Clinical Diagnoses:

1. Chronic vascular disease of unknown type. Question of chronic glomerulonephritis with acute exacerbation of glomerulonephritis in the terminal phase.
2. Possible periarteritis nodosa with predominant renal lesions.
3. Gastric ulcer, active, and healed duodenal ulcer.
4. Hypertensive cardiovascular disease.
5. Vitiligo.

Pathologic Diagnoses:

1. Respiratory: Tracheobronchitis, pulmonary emphysema (bilateral), with large blebs in the right apex; pulmonary atherosclerosis; bilateral pleural effusion.
2. Cardiovascular: Coronary atherosclerosis; aortic atherosclerosis; myocardial hypertrophy of the left ventricle; myocarditis with abscess formation; fibrinopurulent pericarditis, and pericardial effusion.
3. Liver: Chronic passive congestion and focal hepatitis.
4. Spleen: Chronic passive congestion and acute splenitis.
5. Gall-bladder: Chronic cholecystitis.
6. Gastrointestinal tract: Nonperforated gastric ulcer, 1 cm. in diameter in lesser curvature.
7. Adrenal glands: Cortical nodular hyperplasia.
8. Musculoskeletal system: Pyogenic abscess, first right intercostal space.
9. Genitourinary tract: Chronic glomerulonephritis associated with acute pyelonephritis and arterionephrosclerosis.

Description of the Kidneys: The right kidney weighed 170 gm. and the left 190 gm. The capsule was slightly thickened and revealed a grossly irregular cortex due to the presence of large 1 to 2 cm. yellow protuberant masses. When cut, these abscesses contained a deep yellow thick purulent material. In the section the capsule was thickened and infiltrated with chronic inflammatory cells. Interstitial tissue in many areas showed infiltration with inflammatory cells, and in some areas there were large collections of these which took on the appearance of frank abscesses. For the most part, glomeruli showed loss of architecture, and there was a merging of the loops into one another so that the tuft appeared as one hyalinized mass. In some areas Bowman's space was partially to completely obliterated; in others, it appeared to be normal. Some glomeruli showed definite epithelial proliferation, with the formation of typical crescents. The blood vessels showed marked intimal thickening.

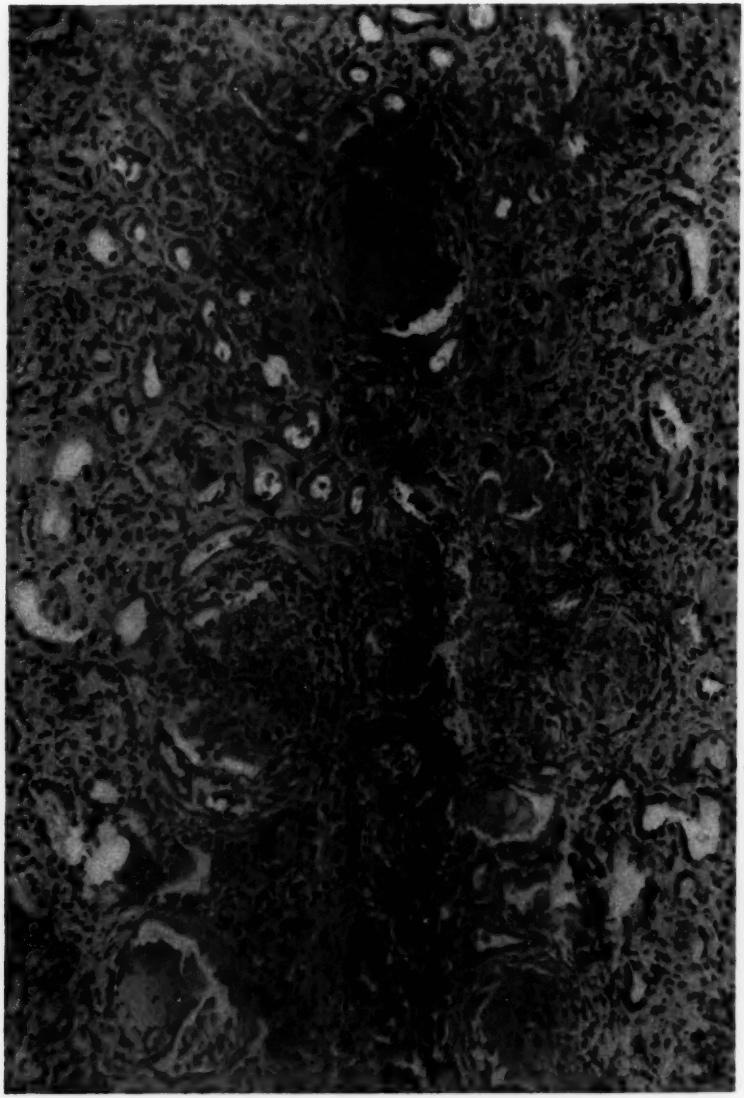

FIG. 3C. Photomicrograph (78×) of renal cortex of case 3. Interstitial inflammatory reaction and changes of pyelonephritis are superimposed upon the primary changes of fibrosis and crescent formation in the glomeruli.

The over-all microscopic picture was one of chronic glomerulonephritis with superimposed acute pyelonephritis. These findings are illustrated in figure 3c.

Discussion

Acute glomerulonephritis in the inflammatory stage, or acute exacerbations of a chronic glomerulonephritis, are characterized by urine sediments showing large amounts of red cells, the characteristic red cell or blood cast, and chemical tests for blood in the urine, such as a positive benzidine test. Some albumin and other types of hyaline casts may be present. In the nephrotic syndrome massive albuminuria is a common finding, and protein excretion in excess of 8 gm. per 24 hours is quite usual. Large numbers of hyaline casts are found. The emphasis in examination of the sediment is usually placed on tubular elements, with a finding of many cellular casts containing vacuoles and in various stages of cellular degeneration. Oval fat bodies may be stained with Sudan stain. Doubly refractile fat bodies manifested by the characteristic Maltese cross appearance are seen when the sediment is examined under the polarizing microscope.[20] Numerous renal epithelial cells may also be found. In chronic degenerative stages of glomerulonephritis the albuminuria tends to diminish in quantity along with the diminishing glomerular filtration rate and the decrease in specific gravity of the urine. The significant development is the appearance of the broad cast or renal failure cast, which is generally ascribed to grossly dilated renal tubules, when much scar tissue and loss of renal parenchyma have ensued.

These three classic stages of glomerulonephritis generally extend over many years. Indeed, as long as 30 to 40 years may be required to run out the natural history of glomerulonephritis. The term "telescoped urinary sediment" simply refers to the fact that these three stages, usually separated in time, are represented in a single urinary specimen. While description of this sediment has performed a valuable service in focusing attention on an important diagnostic aid in patients with visceral angiitis, it is rather surprising to have it considered a rarity in chronic glomerulonephritis. The present finding in a single year of three cases of chronic glomerulonephritis demonstrating a telescoped urinary sediment seems to indicate that the appropriate sequence of events is not unusual in the natural history of chronic glomerulonephritis, and that the telescoped urinary sediment should in no sense be considered as pathognomonic of visceral angiitis.

Summary

1. The term "telescoped urinary sediment" refers to the condensation in a single urinary sediment of elements characteristically found in the three classic stages of chronic glomerulonephritis, namely, acute glomerulonephritis, or acute exacerbation, nephrotic syndrome, and the chronic degenerative phase of glomerulonephritis. This sediment has been described as typical of visceral angiitis.

2. Three cases are reported of chronic glomerulonephritis that demonstrated a telescoped urinary sediment, presented a good history and picture of glomerulonephritis, negative tests for lupus erythematosus and periarteritis nodosa, and autopsy findings characteristic of the renal picture of chronic glomerulonephritis with the absence of angiitis in other body organs.

3. Telescoped urinary sediment, while a valuable diagnostic tool, should in no sense be considered as pathognomonic of visceral angiitis.

ACKNOWLEDGMENT

We wish to acknowledge the help of the Renal Residents and the Nursing Staff in carrying out this study. Miss Lois Liddle gave technical assistance.

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CORTISONE THERAPY OF EARLY EPIDEMIC HEMORRHAGIC FEVER: A PRELIMINARY REPORT *

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Introduction

Epidemic hemorrhagic fever (EHF) is an infectious disease of unknown etiology which was first encountered by the U. S. Army in Korea during the spring of 1951. It is characterized by an initial toxic-febrile state with spontaneous petechiae, leukocytosis and thrombocytopenia, followed by variable degrees of renal and cardiovascular involvement. As yet, no specific therapeutic agent has been found for this disease.

A nonspecific beneficial effect from the administration of cortisone in conjunction with the appropriate antibiotic preparation, has been demonstrated in patients ill with typhoid fever,[1] scrub typhus [2] and Rocky Mountain spotted fever.[3] For these patients the toxic-febrile clinical phase is shortened even more than when the specific therapy is employed alone. The thrombocytopenia and abnormal capillary fragility of other diseases [4, 5] have disappeared during treatment with this hormone. Since a toxic-febrile state, disturbances of capillary function and thrombocytopenia are all characteristic of epidemic hemorrhagic fever, it seemed possible that some benefit might be obtained by the administration of cortisone.

The experience of Katz and his associates [6] had led them to conclude that cortisone and corticotrophin were of little or no value in the treatment of this disease. It may be noted, however, that many of these patients were given hormonal therapy after the disease was well established, i.e., after onset of proteinuria and azotemia and even after the appearance of shock in some patients.

On the premise that maximal benefit could be expected only if cortisone was given before the development of severe tissue damage, Woodward and members of our group reëxamined the problem during the fall of 1953.[7] They treated 39 patients suspected of having hemorrhagic fever with a combined regimen of cortisone and Terramycin, or with Terramycin alone; all members of the group had been ill for less than 72 hours when therapy was begun. The preliminary observations clearly indicated that cortisone given under these conditions did not dramatically obliterate the disease, but did suggest that it moderated the course of the illness. Furthermore, no evidence was forthcoming of harmful effects on the patients which could be attributed to the cortisone therapy.

* Received for publication September 17, 1954.

An additional impetus to extension of the trial of cortisone was given by the preliminary observations of Greisman and Moe,[8] which indicated that a vasodilator substance was present in plasma of hemorrhagic fever patients. This substance, which induced dilation of the small vessels in the rabbit's eye, presumably played a part in the capillary dilation, decreased vasomotion, diminished blood flow and frank hemorrhage observed in the nail-fold capillary beds of patients during the early stages of epidemic hemorrhagic fever.[9] Both in patients and in experimental rabbits these vascular phenomena could be temporarily inhibited by large doses of cortisone.

The present report is therefore concerned with an evaluation of the effects of cortisone given early in the course of epidemic hemorrhagic fever.

Method of Study

Selection of Patients: All patients entering the Hemorrhagic Fever Center, Korea, during the period from October 29, 1953, to December 15, 1953, were examined immediately or within a few hours after admission and included in the study if the criteria for establishing the diagnosis of hemorrhagic fever suspect (listed in table 1) were fulfilled. Occasional patients were excluded when the language barrier prohibited an accurate history, or if a definite contraindication for cortisone therapy was present, e.g., furunculosis, pneumonia, etc. Upon acceptance for study, each patient was designated to receive lactose if the last digit of his military serial number was odd, or cortisone if even.

Final Diagnosis: Seventy-three patients were admitted to the study. Five of these were subsequently shown to have some disease other than

Table 1

Epidemic Hemorrhagic Fever Criteria for Suspect Patients
Early Febrile Phase (0 to 72 Hours of Illness)

Manifestations	
Major	**Minor**
1. Exposure—endemic area	1. Anorexia
2. Fever (100° or above)	2. Nausea and vomiting
3. Acute onset	3. Malaise
4. Headache—retro-orbital	4. Feverishness and chilliness
5. Conjunctivitis	5. Normal white blood cells or moderate leukopenia
6. Pharyngeal injection without soreness	
7. Periorbital fullness	
8. Facial flush	
9. Petechiae	
10. Backache	

Requirements for Selection as Early Febrile Epidemic Hemorrhagic Fever Suspect

A. First and second major manifestations with at least three additional major and three minor manifestations.
B. No evidence of other disease.
C. Normal chest x-ray.

Note: Only patients meeting these criteria were included in this study.

TABLE 2
Final Diagnoses of All Patients

Treatment	Total Patients	Other Diagnoses*	Fever of Unknown Origin	Confirmed Epidemic Hemorrhagic Fever
Lactose	38	4	8	26
Cortisone	35	1	12	22

* One patient treated with cortisone was subsequently diagnosed as asymptomatic streptococcic pharyngitis. The other diagnoses in the lactose group were: (a) pulmonary tuberculosis, (b) infectious mononucleosis (two patients), and (c) infectious hepatitis.

epidemic hemorrhagic fever, or fever of unknown origin (FUO) (table 2), and were excluded from further consideration. Treatment was begun within 72 hours of onset of illness in the 68 patients retained in the study group. The calendar day of disease on which the initial medication was given to these 68 persons was as follows: second day, seven in the lactose group and eight in the cortisone group; third day, 20 in the lactose and 21 in the cortisone group; fourth day, seven in the lactose and five in the cortisone group.

The records of all 68 patients were reviewed after the patient had been discharged from the hospital to decide whether the final diagnosis would be "EHF confirmed" or "FUO." A given patient was considered to be a confirmed case of epidemic hemorrhagic fever if, in addition to meeting the requirements listed in table 1, he displayed two of the four findings listed below: (1) blood urea nitrogen values of at least 25 mg. per 100 c.c. on two or more days of disease; (2) proteinuria of at least 0.5 gm. per liter of 24-hour urine sample for two or more days; (3) diuresis of not less than 3,000 ml. per 24 hours for two or more consecutive days, and (4) hyposthenuria with specific gravity values of 1.015 or less by concentration test within three weeks of the onset of illness.

A diagnosis of fever of unknown origin was applied to those patients in the study group who did not fulfill the requirements listed above as necessary to convert the diagnosis of epidemic hemorrhagic fever suspect to epidemic hemorrhagic fever confirmed.

Treatment and Care of Patients: Forty-seven of the 68 patients studied were admitted to one ward under the care of two members of our group and the same nursing staff throughout the period of study. This insured uniformity of general care, which was further standardized by employing, insofar as possible, a uniform routine as to bed-rest, ambulation, diet, fluid intake (800 to 1,200 ml. per day in excess of output) and analgesia.

Lactose and cortisone in gelatin capsules of similar appearance were administered by mouth every six hours, and in those instances when oral cortisone was not retained, equal dosage was substituted by the intramuscular route. A total of 1,100 mg. of cortisone was given over a period of five days according to the following schedule: 300 mg. daily for the first two days, 200 mg. daily on the third and fourth days, and 100 mg. on the fifth day.

Though efforts were made to conceal the identity of the drug under investigation, these were not entirely successful. In the first place, lactose was not administered intramuscularly to those members of the control group who vomited their oral medication. Furthermore, after the first few days the physicians generally were able to guess which medication was being given because of subjective and objective improvement in many of the patients receiving cortisone.

Laboratory Studies: Quantitative 24-hour urinary protein determinations, blood urea nitrogen values, and total and differential white blood cell counts were obtained daily in all patients in the study. Platelet counts were made daily on nine patients of each treatment group. In addition, the usual laboratory tests were carried out. All routine laboratory examinations were made by the procedures described in the Department of the Army Technical Manual TM 8-227 (August 8, 1951).

General Procedures: Patients were seen prior to the beginning of therapy and daily thereafter by one of our group not directly responsible for the care of these patients; this investigator, unaware of whether a given patient was receiving lactose or cortisone, recorded the absence or presence and the severity of signs and symptoms.

A patient was considered febrile if he exhibited an oral temperature above 99° F. The upper limit of normal for blood urea nitrogen values was designated 24 mg. per 100 c.c. in order to exclude these values above 20 mg. per 100 c.c. occasionally encountered in dehydrated patients. Anuria was defined as no recorded urinary output, oliguria as less than 500 ml. per 24 hours, and onset of diuresis as the day of disease on which urinary output reached or exceeded 2,000 ml. In all instances the source of these data was the nurses' records.

Patients with clinical manifestations of circulatory instability and a systolic pressure of less than 90 mm. Hg were considered to have shock. The shock state was arbitrarily subdivided into mild, severe and irreversible stages with the aid of the following objective findings: (1) diastolic blood pressure less than 50 mm. Hg; (2) pulse rate greater than 100 per minute; (3) hematocrit higher than 60, and (4) pulse pressure less than 15 mm. Hg. A patient was considered to have mild shock if, in addition to the basic criteria for shock, he presented one of these four additional findings, or severe shock if two or more of these findings were present. Irreversible shock was defined as that form of severe shock that did not respond to the administration of concentrated serum albumin and l-norepinephrine.

Statistical Analysis: All data presented in this study were analyzed for statistical significance. The "T" test was employed with respect to measurements, i.e., azotemia, proteinuria, fever, etc. Mean values were not considered significant unless they were two and one-half times the standard error. All enumerative differences between the two treatment groups, such as incidence of patients diagnosed as fever of unknown origin, and distribu-

tion of patients experiencing shock, were evaluated by the Chi Square (X^2) method and were considered significant at the 1% level. Those differences that were found to be significant are so designated in *Results*.

Results

Severity of Initial Disease in Treated Groups: The severity of the disease was essentially the same in the patients of the two treatment groups prior to institution of therapy. This was established by evaluation of signs

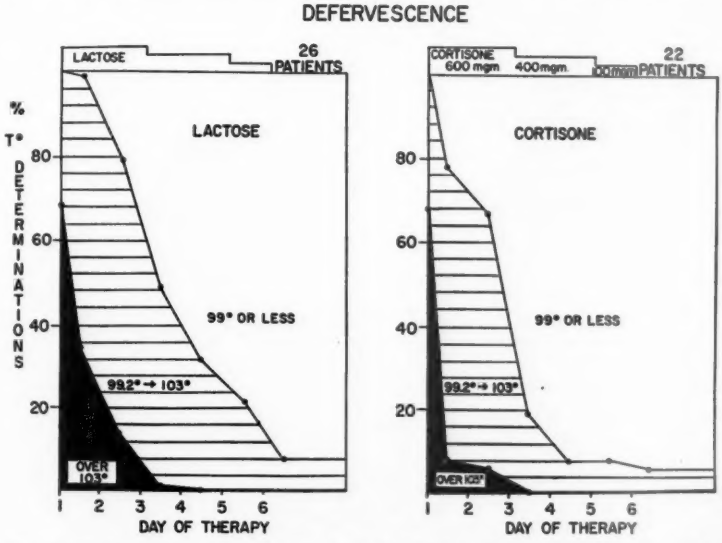

FIG. 1. Defervescence: Showing per cent distribution of oral temperatures on admission as well as the four highest determinations during each subsequent day of therapy. Initial drug dose administered to all patients within six hours of admission and prior to the seventy-second hour of illness.

and symptoms of illness by one of our group who did not know which drug would be administered to a given patient, and subsequent review of the maximal temperature, occurrence of leukocytosis, and degree of qualitative proteinuria on admission to the hospital. At the time the first quantitative urinary protein determinations were obtained, as shown in figure 2, 26% of the values for the lactose group were in the range of severe proteinuria, while only 6% of such values fell in this range for the cortisone-treated group. It should be emphasized that these determinations followed 24 hours of therapy, and therefore do not indicate any discrepancy regarding the initial severity of the disease in the two treatment groups. Furthermore, as illustrated in figure 3, azotemia, which generally develops somewhat later than proteinuria, was comparable in the two groups 24 hours

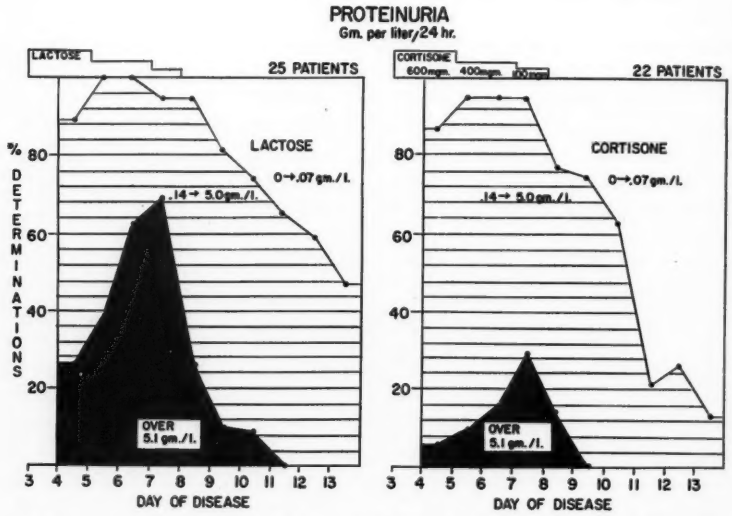

FIG. 2. Proteinuria: Showing per cent distribution of insignificant (0 to .07 gm./liter), moderate (.14 to 5.0 gm./liter), and severe (over 5.1 gm./liter) quantitative urinary protein determinations on total 24-hour specimens by day of disease. Prior to onset of therapy there was no appreciable difference between the two groups of patients regarding qualitative proteinuria.

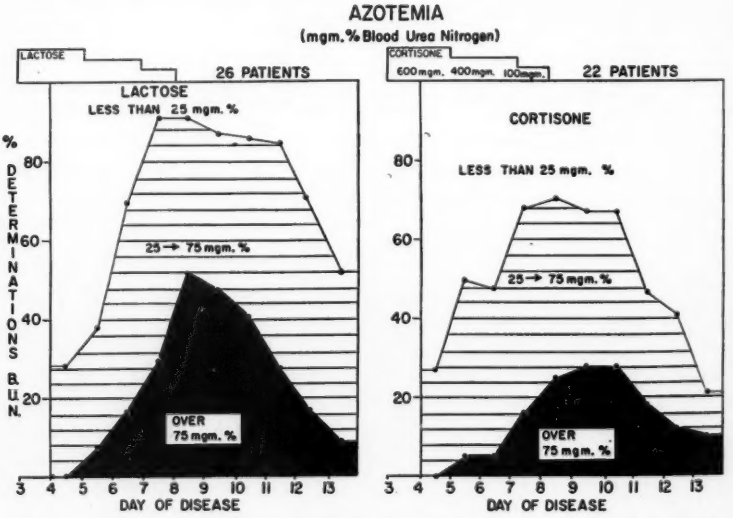

FIG. 3. Azotemia: Showing per cent distribution of daily blood urea nitrogen determinations by day of disease. Therapy initiated for all patients prior to the seventy-second hour of disease. The above determinations began after 24 hours of drug administration.

after onset of therapy. The mean day of disease on which treatment was begun was 2.9 for both groups. Equitable distribution of patients with severe disease is suggested by the occurrence of four patients in each group who were unable to tolerate oral medication during an appreciable part of the study period.

General Observations on Treated and Control Groups: It may be pointed out immediately that certain definite differences were noted in the responses of the two groups of patients, and that in general those persons receiving cortisone enjoyed a milder course of illness. However, the disease in the majority of patients in the cortisone group pursued its customary progress [10] through the usual phases, i.e., febrile, hypotensive, oliguric and diuretic, and the ultimate mortality in the two groups was about the same.

Seventy-three patients were included in the study as epidemic hemorrhagic fever suspects according to the criteria listed in table 1 and discussed under *Method of Study.* Thirty-eight patients received lactose and 35 patients were treated with cortisone.

Since specific laboratory diagnostic procedures for epidemic hemorrhagic fever did not exist, both the lactose and the cortisone groups were carefully evaluated on clinical grounds to determine which patients in the study should receive a final diagnosis of epidemic hemorrhagic fever confirmed or fever of unknown origin or, finally, which patients had a recognizable disease that could receive some other specific diagnosis. The criteria employed for establishing the diagnosis of epidemic hemorrhagic fever confirmed are presented in *Method of Study.* As indicated in table 2, one patient treated with cortisone and four patients who received lactose had illnesses which were neither epidemic hemorrhagic fever nor fever of unknown origin. Of the 34 patients remaining in each group, 22 patients treated with cortisone were diagnosed as epidemic hemorrhagic fever confirmed, compared to 26 of the patients who received lactose (table 2).

Any therapeutic agent which exerted a dramatic curative effect early in the course of the illness might be expected to result in obliteration of the disease or in its modification to such an extent that the majority of treated patients would fail to meet the clinical criteria for confirmation of the diagnosis. Therefore, the incidence of fever of unknown origin assumes importance. Eight patients who received lactose and 12 patients treated with cortisone were eventually designated as fever of unknown origin. If a medication was partially successful in influencing the course of hemorrhagic fever, then one would assume that the earlier it was administered, the more likely it would be to change the clinical picture. It is of interest that, of the eight patients in the cortisone group who were initially treated on the second day of disease, six were eventually diagnosed as fever of unknown origin. In contrast, three of the seven admitted to the lactose group on the second day of illness were finally classified as fever of unknown origin. No such difference was noted in the distribution of patients designated fever of unknown origin among those treated first on the third

day; thus, six of the 21 in the cortisone group were so diagnosed, and four of 20 in the lactose group. The remaining patients considered to have had fever of unknown origin entered the lactose group on the fourth day of disease. There is no statistically significant difference between the total number of fevers of unknown origin in the two treatment groups or in the numbers in the two groups who were begun on therapy on the second day of illness. Nevertheless, the results are of interest and suggest the desirability of accumulating larger groups.

For the present, then, it may be said that if cortisone therapy modified the disease sufficiently to render it unrecognizable, it did so only in those patients who were treated shortly after the onset of illness, i.e., the second day of disease in the current study.

TABLE 3

Fatalities in Treated Groups

Treatment*	No. of Patients Confirmed Epidemic Hemorrhagic Fever	No. of Deaths	Day of Disease	Cause of Death
Lactose	26	2	5	a) Irreversible shock
			7	b) Irreversible shock
Cortisone	22	3	10	c) Massive gastrointestinal hemorrhage
			14	d) Bilateral bronchopneumonia, and mucopurulent tracheobronchitis
			17	e) Bronchopneumonia, mucopurulent tracheobronchitis, and slight pulmonary edema

* Therapy of five days' duration instituted for all patients prior to the seventy-second hour of disease.

Despite the fact that the mortality rates in the treated and control groups were not significantly different, it may be seen in table 3 that patients in the cortisone group who did succumb lived longer and died of causes different from those in the control group.

In general, the manifestations of hemorrhagic fever directly associated with the death of patients are shock, pulmonary edema, uremia with hyperkalemia and acidosis, and massive hemorrhage.[10] Complications which not uncommonly occur terminally in severely ill patients with hemorrhagic fever are similar to those in other debilitated patients and include bacterial infections such as bronchopneumonia.

The two deaths in the control group with irreversible shock on the fifth and seventh days, respectively, and the fatality in the cortisone group from massive hemorrhage on the tenth day would appear to be direct results of hemorrhagic fever. On the other hand, the two additional deaths in the cortisone group which occurred on the fourteenth and seventeenth days, respectively, associated with obstructive mucopurulent tracheobron-

chitis and bronchopneumonia, appear only indirectly related to hemorrhagic fever. Indeed, both patients seemingly were recovering from hemorrhagic fever when they developed these pulmonary complications.

Fever: Patients treated with cortisone exhibited a more rapid resolution of fever than those who received lactose (figure 1). Not only did severe pyrexia (greater than 103° F.) subside more promptly in the cortisone group, but also, by the fourth day of therapy, 15 of the 22 patients in the cortisone group were afebrile (99.0° F. or less), while only seven of the 26 patients in the lactose group had normal temperatures. Four of the 22 patients treated with cortisone experienced prompt and lasting defervescence within 24 hours of the onset of therapy. Eleven of the 26 patients who received lactose exhibited resolution of fever by lysis within 48 to 72 hours after initiation of therapy, as did the remaining 18 cortisone-treated patients. The balance of the patients (15) of the lactose group all exhibited a more gradual defervescence, covering periods ranging from 84 to 144 hours from the initial dose of lactose (figure 1).

Return of fever on the eighth or ninth day of disease, i.e., within one day of cessation of special drug therapy, occurred in six patients who received lactose and seven of those treated with cortisone. This was accompanied by evidence of secondary bacterial infection in a few instances. Return of hemorrhagic fever symptoms (see following paragraph) accompanied return of fever in four of the seven cortisone-treated patients on the last day of therapy or within the subsequent 24 hours, but this was not observed in the six patients who received lactose.

Symptomatic Response: The toxic symptoms of rigor, feverishness, cephalic flush, retro-orbital headache, photophobia, painful ocular motion, lumbar pain, anorexia, nausea, vomiting and somnolence are common features of the febrile phase of epidemic hemorrhagic fever. In the more severely ill patients delirium or psychic agitation frequently supervenes.

In general, symptomatic relief was directly related to defervescence. Thus, the four cortisone-treated patients who became afebrile within 24 hours after initial therapy also experienced prompt and complete relief of all symptoms. This symptomatic relief was less dramatic in the remaining cortisone-treated patients but was still quite evident when compared to patients with similar duration of fever who had received lactose. This is exemplified by the observation that the ward physicians (B. U. and R. C. B.), early in the study period when they did not know in which therapy group a given patient belonged, could generally guess the correct answer on the basis of the symptomatic response.

Vomiting, not infrequently accompanied by hematemesis, occurs during the toxic-febrile phase (first through the sixth day of disease), as well as during the azotemic phase (fourth through the eleventh day), and assumes specific importance when one considers that the water and electrolyte balance of hemorrhagic fever patients is often precarious. It is impressive, therefore, that vomiting at any time during hospitalization was recorded

for only seven of the 22 cortisone-treated patients, while 15 of the 26 patients who received lactose suffered from this manifestation. A total of 21 and 59 patient days of vomiting was recorded in each of the respective groups.

The contrast in severity of the often excruciating headache and backache suffered by patients in the two groups may be illustrated by the average amount of codeine required for relief during the five day period of drug therapy. This was 5.5 grains for each of 24 patients who received lactose, compared to 2.4 grains for each of the 15 cortisone-treated patients who required analgesia. Only two patients of the lactose group required no analgesia, compared to seven of the cortisone group.

Urinary Output: Anuria (table 4) was observed in seven patients who received lactose and in two treated with cortisone. None of the five fatalities in the two groups was directly related to renal failure. However, two

TABLE 4

Anuria in Treated Groups

Treatment	No. of Patients	Number of Patients with Anuria
Lactose	26	7*
Cortisone	22†	2‡
Total	48	9

* Two patients died of irreversible shock, while anuric, on the fifth and seventh days of disease.

† One patient not exhibiting anuria died on the fourteenth day of disease of pulmonary complications (see table 3).

‡ One patient died of massive hemorrhage on the tenth day, and one patient who died of pulmonary complications on the seventeenth day had passed from anuria to diuresis.

patients, both in the lactose group, experienced anuria of sudden onset, i.e., without antecedent oliguria, during the course of irreversible shock. The remaining anuric patients, five in the lactose group and two in the cortisone group, displayed oliguria for a day or so before becoming anuric. Oliguria (less than 500 c.c./24 hr.) without complete suppression of urine formation at any time occurred in 12 of the patients who received lactose and in 10 of those given cortisone.

The mean day of disease on which onset of diuresis (2,000 c.c. of urine/24 hr.) occurred was 8.3 (range four to 11) for the lactose group and 7.3 (range five to 12) for the cortisone group. This difference is not statistically significant.

Circulatory Status: Circulatory collapse, often precipitous, is a frequent feature of epidemic hemorrhagic fever and usually occurs on the fourth to seventh days of illness. A high hematocrit, tachycardia, decrease of systolic or diastolic blood pressures, or both, warm extremities, and narrow pulse pressure are signs of this form of shock and occur in such variable combinations that any precise definition would be, at best, controversial. Ac-

cordingly, for purposes of this study, shock was considered as an alteration of the cardiovascular status manifested by some or all of the signs previously mentioned. Mild, severe and irreversible stages of shock are defined in *Method of Study* (table 5).

Ten of the 48 epidemic hemorrhagic fever patients in the entire study presented evidence of shock, and of this group three were treated with cortisone and the remaining seven received lactose. The failure of appearance of irreversible shock (table 5) in the cortisone group is also interesting, but

TABLE 5

Circulatory Status

Drug Administered	Total No. Patients	Mild Shock	Severe Shock	Irreversible Shock
Lactose	26	2	3	2*
Cortisone	22	1*	2*	0

* All of these patients died, but those in the cortisone group recovered from shock and subsequently died of complications (see table 3).
† Definitions of the stages of shock are presented in *Method of Study*.

a greater number of patients would be required to establish the significance of these observations.

Laboratory Data: A distinct difference is evident (figure 2) between the lactose and the cortisone groups with regard to severe (greater than 5.1 gm./L.) and insignificant (0 to .07 gm./L.) degrees of proteinuria as determined in 24 hour specimens of urine. In addition, there was a marked disparity between the two groups when one considers the total protein excreted during the entire course of the disease (table 6). The mean duration

TABLE 6

Total Excretion of Urinary Protein by Recovered Patients

Treatment	Total Patients*	Grams Proteinuria		
		5 to 20	20 to 40	Over 40
Lactose	23	4	13	6
Cortisone	19	13	5	1

* Data on the five fatal cases not included. One patient in the lactose group is omitted because of failure to obtain adequate 24-hour urine specimens.

of proteinuria was 8.7 (range, three to 21 days) for the patients who received lactose, and 5.9 days (range, two to 11 days) for those who were treated with cortisone; statistically, this is a significant difference.

Blood urea nitrogen determinations indicating severe azotemia (greater than 75 mg. per 100 c.c.) were appreciably more frequent in the lactose group as the disease progressed than in the cortisone group (figure 3). The incidence of determinations indicating moderate azotemia (blood urea nitrogen of 25 to 75 mg. per 100 c.c.) was about the same until the tenth day of

disease, when these values declined more rapidly in the cortisone group than in the group receiving lactose. Four members of the cortisone group and one of the lactose group failed to develop azotemia at any time during the course of the disease. The upper limit of normal for blood urea nitrogen values was arbitrarily selected as less than 25 mg. per 100 c.c. (see *Method of Study*), instead of employing the usual value of 20.

The mean duration of azotemia was 7.1 days (range, 0 to 15 days) for the patients who received lactose, compared to 4.2 days (range, 0 to 10 days) for those treated with cortisone. These differences in severity and duration of azotemia are statistically significant.

There was no appreciable variation of the serial platelet counts, or the total or differential white blood cell counts when the treated groups were compared. The customary abnormalities of these and other laboratory determinations in the course of epidemic hemorrhagic fever are described elsewhere.[11]

Discussion and Summary

The rationale for employing cortisone as adjunctive therapy in the early treatment of epidemic hemorrhagic fever has been reviewed.

Sixty-eight patients suspected of having epidemic hemorrhagic fever on the basis of standard clinical criteria were given either lactose or cortisone. In all patients, treatment was initiated prior to the seventy-second hour of disease. Total dosage and duration of cortisone therapy for each of the 34 patients who received this hormone were 1,100 mg. for a period of five days.

No untoward sequelae attributable to cortisone were observed, and the majority of the cortisone-treated patients progressed through the usual phases of epidemic hemorrhagic fever. In addition, the ultimate mortality of the cortisone and lactose groups of patients was essentially the same. Therefore, it can be said that cortisone exerted neither a specific therapeutic effect nor a detrimental influence in this disease.

Nonetheless, as has been demonstrated by the administration of cortisone to patients with certain other diseases, some beneficial results were obtained. A distinct amelioration of the toxic-febrile clinical state, as well as significant reductions of the severity and the duration of both proteinuria and azotemia, was obtained. Evidence was also recorded which suggests that the renal insufficiency and cardiovascular collapse of epidemic hemorrhagic fever are favorably influenced by early cortisone therapy.

The present results are interpreted as sufficient to justify further studies of the effects of cortisone when administered early in the course of epidemic hemorrhagic fever.

Acknowledgment

The support of the Commission on Hemorrhagic Fever of the Armed Forces Epidemiological Board is acknowledged, as well as the help of Dr. J. Dingle, Dr. J. E. Smadel and Dr. T. E. Woodward in planning the study and summarizing the observations. The

study could not have been accomplished without the interest and coöperation of the medical and nursing staff of the 48th Surgical Hospital, Mobile Army, as well as the aid of the Medical Sections of Eighth Army and the Far East Command.

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THE SOURCES OF UPPER GASTROINTESTINAL BLEEDING IN LIVER CIRRHOSIS *

By Angelo Dagradi, M.D., F.A.C.P., *Long Beach, California,* Donald Sanders, M.D., *Salem, Oregon,* and Stephen J. Stempien, M.D., *Beverly Hills, California*

Introduction

The occurrence of upper gastrointestinal hemorrhage in patients suffering from hepatic cirrhosis represents a serious complication of this disease. Prognosis in this situation is usually dependent upon the extent of the antecedent liver disease and upon the severity of the additional acute hepatocellular injury produced by the bleeding episode. The latter factor is in turn dependent upon the efficacy of the measures taken to control the bleeding and counteract shock, and upon the etiology of the source of the bleeding. In this report we wish to stress the importance of accurately determining the nature of the bleeding lesion in these patients, both because of its importance in assessing the prognosis and for the institution of proper emergency and definitive therapy. To this end, diagnosis depends upon the judicious use of roentgenography and endoscopy. We have been particularly impressed by the diagnostic value of both esophagoscopy and gastroscopy when used as adjuncts to roentgenography.

Method of Study

A review of our endoscopic protocols reveals that during the period January 1, 1950, through July 31, 1953, esophagoscopic and gastroscopic examinations, alone or in combination, were performed at this hospital on a total of 121 patients with hepatic cirrhosis. Of this group, endoscopy was performed in 92 patients because of the presenting complication of gross upper gastrointestinal hemorrhage manifested by either hematemesis or melena, or both. The diagnosis of hepatic cirrhosis was confirmed by liver biopsy with the Vim-Silverman needle in 32 patients and by postmortem examination in 33 patients. In the remaining 56 patients the history, physical examination, laboratory findings and clinical course were characteristic of hepatic cirrhosis. The liver function tests were grossly deranged in all but three cases, and in the latter, liver biopsy substantiated the diagnosis.

Our initial efforts were primarily aimed toward rapid control of the bleeding. Roentgenologic examination, using the Hampton technic, was performed shortly after the stabilization of the blood pressure, red blood

* Received for publication September 20, 1954.

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cell count, hemoglobin and hematocrit. We utilized the Schindler esophagoscope and gastroscope for our endoscopic examinations. In a few cases endoscopic examinations were done during the phase of active bleeding, but in most such instances we have been unsuccessful in conducting a satisfactory examination because of the coating of the objectives of the optical systems by the blood. As a consequence of this experience we have made it a practice to carry out endoscopic examinations shortly after the active bleeding has been controlled. Esophagoscopy was usually performed first, and if this failed to disclose the source of bleeding, gastroscopy was then accomplished. In many cases, when the radiologic examination failed to demonstrate an esophageal lesion, gastroscopy was done initially, and this method was used also for examination of the lower third of the esophagus. We have encountered three instances where gastroscopic examination revealed the presence of varices in the cardiac portion of the stomach when the initial esophagoscopic examination had failed to demonstrate varices. This indicates the importance of a combined endoscopic approach in selected cases.

In only two instances was bleeding reactivated during or following instrumentation, and in neither case was the bleeding of a serious nature.

Results

Table 1 summarizes the sources of upper gastrointestinal bleeding and their incidence in our series of 92 patients with hepatic cirrhosis and bleeding. It is of importance to note that esophageal varices were found to represent the source of bleeding in only 38% of our patients, while in 62% the lesion lay elsewhere. Of equal importance is the fact that bleeding from hemorrhagic gastritis occurred in 31.5% of the cases, which is an incidence almost equal to that of esophageal varices. Gastroduodenal ulcer was responsible for bleeding in 13.1% of our cirrhotic patients.

The prognostic value of making an accurate determination of the source of the upper gastrointestinal bleeding in patients with liver cirrhosis is de-

Table 1

Sources of Upper Gastrointestinal Bleeding and Their Frequency in Patients with Liver Cirrhosis

Source	Number	Per Cent	Number	Per Cent
Esophageal (and cardiac varices)	35	38.0		
Undetermined	13	14.1		
All other causes	44	47.9		
Hemorrhagic gastritis			29	31.5
Duodenal ulcer			11	12.0
Hiatal hernia			2	2.2
Gastric ulcer			1	1.1
Leukemic infiltration			1	1.1
Total	92	100.0	44	47.9

TABLE 2

Sources of Upper Gastrointestinal Bleeding in Individuals with Liver Cirrhosis: Comparison between Surviving and Deceased Patients

Diagnosis	Surviving Patients		Deceased Patients	
	Number	Percentage	Number	Percentage
Varices	12	34.3	23	65.7
Hemorrhagic gastritis	27	93.1	2	6.9
Undetermined	10	77.0	3	23.0
Duodenal ulcer	10	91.0	1	9.0
Hiatal hernia	2	100.0	0	0.0
Leukemic infiltration	0	0	1	100.0
Gastric ulcer	1	100.0	0	0.0
Total	62		30	

picted in table 2, which demonstrates very strikingly the serious portent of bleeding when it stems from esophageal varices (65.7% of our patients with varices died during the period of this study). On the other hand, when the source of bleeding is from sites other than varices, the prognosis is much more favorable (12.3% mortality in 57 patients). The mortality rate in patients with hemorrhagic gastritis was 6.9%.

DISCUSSION

It is self-evident that an accurate determination of the source of bleeding in liver cirrhosis is important for the determination of the proper emergency and definitive therapy. Much too often it is assumed that a patient who bleeds and has liver cirrhosis is bleeding from esophageal varices. One striking example of such an erroneous assumption occurred at this hospital in a case in which the emergency management was entirely confined to a tamponade of the lower esophagus and cardia without due attention to the necessity of making an accurate diagnosis. In this particular case the postmortem examination disclosed that the bleeding came from a benign gastric ulcer. It is therefore important that in a patient who bleeds and has liver cirrhosis all of the causes of gastrointestinal bleeding should be considered. Palmer and Brick [1] have called attention to the importance of this diagnostic problem in liver cirrhosis and bleeding. In their series of patients, 27% were examined gastroscopically but only three cases were found to have erosive gastritis which could account for hemorrhage. The authors, however, wisely point out that this is not a true indication of the incidence of this lesion. In contrast to their findings, 50% of our patients were gastroscoped, giving an incidence of 31.5% with hemorrhagic erosive gastritis.

CONCLUSIONS

1. The commonest sources of upper gastrointestinal bleeding in liver cirrhosis are esophageal varices, hemorrhagic gastritis and duodenal ulcer.

2. Hemorrhagic gastritis ranks almost equally with varices as a frequent cause of bleeding in cirrhosis of the liver.

3. The differential diagnosis of bleeding in liver cirrhosis should include all of the bleeding lesions common to noncirrhotic patients in addition to esophageal and gastric varices.

4. Esophagoscopy and gastroscopy are important adjuncts in the diagnostic study of upper gastrointestinal hemorrhage in liver cirrhosis.

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PHEOCHROMOCYTOMA: TWO CASE REPORTS WITH UNUSUAL REACTIONS AND A GENERAL REVIEW *

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Case reports of pheochromocytomas have been appearing with increasing frequency since Labbe [1] in 1922 first pointed out the clinical picture of hyperepinephrinemia associated with these tumors. Recent interest in the etiology and pathogenesis of hypertension has led to the discovery and removal of many of these tumors. Several pharmacologic tests have been developed to aid the establishment of this diagnosis in the past decade. Histamine, mecholyl bromide and tetraethylammonium bromide have been used to stimulate the release of pressor substances from the tumors; thus, a paroxysm of hypertension and symptoms are precipitated. Benzodioxane, Dibenamine and Regitine have been used to combat the effects of these substances; thus, persistent hypertension and symptoms are reduced. Increasing numbers of false-positive and false-negative results are being reported for each test. Both of the cases to be presented had paroxysmal attacks of headache and hypertension. The first case reacted in a paradoxic manner to several tests, while the second case reacted in the expected manner. At the time the first case was studied, these unusual responses had not been reported. Both patients developed an attack of hypertension during the sodium amytal sedation test. To our knowledge, this response has not been reported. The purpose of this paper is to report these unique responses and to review briefly the general subject of pheochromocytoma.

Case Reports

Case 1. A 31 year old white male rayon plant worker was admitted first to the Richmond Veterans Administration Hospital on December 21, 1949, complaining of severe, recurrent, throbbing, bitemporal headaches of one year's duration. These headaches had occurred almost entirely at night, and had awakened him often several times in a single night. Relief was afforded usually within 10 minutes by sitting up or walking. Occasionally, excitement and even small amounts of alcohol had precipitated severe attacks. Recently, attacks lasting several hours had occurred.

His occupation frequently exposed him to carbon disulfide; however, monthly examinations by the company medical department had failed to reveal evidence of intoxication. He suffered from an obvious emotional dilemma which was related to his only child, who had cerebral palsy.

Admission physical examination was entirely normal except for a blood pressure reading of 180/110 mm. of Hg. He had a mild headache at that time. Examination

* Received for publication August 30, 1954.

From the Department of Medicine, McGuire Veterans Administration Hospital, Richmond, Virginia.

† Deceased.

of the eyes revealed only mild astigmatism. All laboratory studies, including complete blood count, urinalysis, spinal fluid examination, routine blood chemical tests, and roentgenograms of the head, cervical spine, sinuses and chest, were normal.

He continued to have headaches, particularly at night, up until one or two days prior to discharge. Recumbency so markedly accentuated his headache during one episode that he had to remain in the upright position for the entire night. Codeine and aspirin and digital pressure over the vessels in the temporal and occipital areas failed to bring relief. Neither amyl nitrite nor ephedrine sulfate, given during a headache-free period, precipitated an attack of headache. His blood pressure was recorded once daily and varied from 100/60 to 180/110 mm. of Hg. On the day of discharge his blood pressure was 100/60 mm. of Hg and he was asymptomatic. He was advised to avoid exposure to carbon disulfide and to procure glasses for astigmatism. It was thought that his headaches were most likely related to nervous tension.

He was re-admitted on May 3, 1950, because he had continued to have headaches, as elaborated above, almost nightly since leaving the hospital. The attacks were severer and of longer duration, and frequently occurred during the day. He had been unable to work for six weeks prior to this admission. Marked pallor had been noted during severe attacks, and following them he was quite weak and sweaty. Further questioning revealed that he had noted an intolerance to heat and had perspired excessively over the past two years. Cafergot had been given, but this accentuated his headache and produced nausea and vomiting.

On admission, complete physical examination failed to reveal abnormalities. He was asymptomatic and his blood pressure was 150/90 mm. of Hg. Complete blood count and blood chemical studies were normal except for fasting glucose levels of 139 mg.% and 145 mg.%. Urinalysis revealed a trace of albumin on several occasions. Urine tested four times daily for one week revealed a trace of sugar on three occasions. An oral glucose tolerance test (100 gm. of glucose) revealed a mild diabetic type of curve. Basal metabolic rates were plus 9% and plus 27%. Tests for adrenal cortical activity were normal.

Electrocardiograms revealed low and diphasic T-waves in the standard leads and in the unipolar leads over the left side of the chest. Repeat x-ray examination of the chest was normal except for slight elevation of the left diaphragm. Intravenous pyelography outlined the urinary tract normally. Body section radiography of both renal regions revealed distinct kidney shadows; however, the adrenal glands or masses in that area were not seen.

Since his blood pressure had varied so widely during the first hospitalization, it was taken at four hour intervals and found to vary from 120/80 to 210/120 mm. of Hg. It was definitely established that his headaches were accompanied by hypertension. Pheochromocytoma was seriously considered, and various tests were made in an attempt to confirm this diagnosis.

On May 16, when his pressure had stabilized at 145/100 mm. of Hg in the recumbent position, he was given 0.05 mg. of histamine base rapidly by vein. There was an immediate drop in blood pressure to 120/70 mm. of Hg, which was followed by a sharp rise to 260 +/170 mm. of Hg (chart 1). The patient had a sensation of increased body warmth immediately after the injection, and this was followed by severe palpitation, severe throbbing headache, nervousness and nausea and vomiting. Patient's headache became so violent that he had to assume the erect position. He stated that this attack exactly simulated one of his more severe spontaneous episodes.

On May 20 the benzodioxane test was carried out, using the technic suggested by Goldenberg.[2] Twenty milligrams of benzodioxane were given intravenously over a period of two minutes, even though his blood pressure was only slightly elevated. It dropped immediately from 160/100 to 140/80 mm. of Hg. This was followed by an immediate rise to 220/114 mm. of Hg. Because of the unusual response, the test

was repeated three days later. There was an immediate drop in both systolic and diastolic pressure of approximately 30 mm. of mercury. Before all the drug had been injected, the pressure rose sharply to 260 +/140 mm. of Hg (chart 2). Again he suffered from severe, throbbing headache and became quite pale, cold and sweaty. There was a tachycardia of 112 during the period of lowered blood pressure, and a bradycardia of 56 during the period of hypertension.

On May 21 the patient was given sodium amytal, 0.2 gm. at hourly intervals for four doses, after which time he slept soundly. The blood pressure rose steadily during sleep to 260 +/170 mm. of Hg (chart 1). Just prior to his awakening his blood pressure dropped to 170/90 mm. of Hg and when he stood erect his blood pressure fell to 120/80 mm. of Hg. He was nervous, fatigued and sweaty. There may have been an initial hypotensive phase which was missed, since his blood pressure was recorded at half-hour intervals.

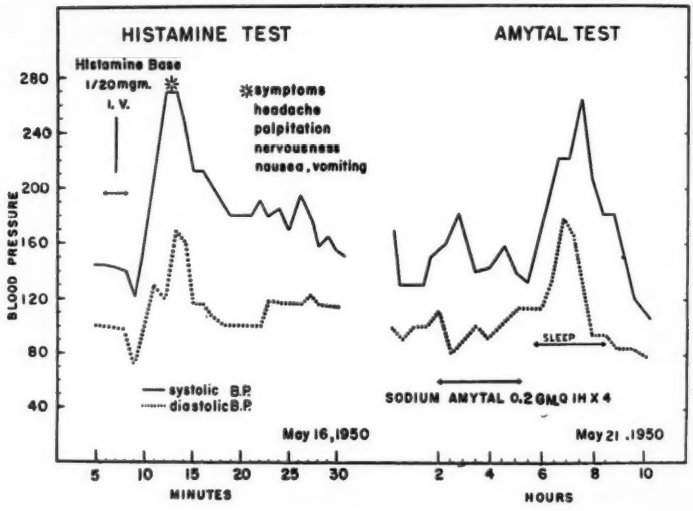

CHART 1.

The cold pressor test produced a rise in both systolic and diastolic pressure of 30 mm. of mercury. Neither headache nor hypertension was produced by five minutes of hyperventilation. On several occasions the patient's blood pressure was stable at 150/100 mm. of Hg while he was supine or sitting, but after he had stood perfectly still for five minutes his blood pressure rose to 240/130 mm. of Hg and he developed headache. Hypertension and headache were relieved by allowing him to walk. Massage and pressure to the right flank produced headache and an elevation of blood pressure to 260 +/140 mm. of Hg on several occasions, while no change was produced by pressure to the left flank.

Since we had no means of controlling severe hypertension which might occur during operation, a small amount of Regitine (C7337) was obtained from Dr. Keith S. Grimson, of Duke University. On June 12, 1950, 0.15 mg. of Regitine per kilogram of body weight (total, 15 mg.) was given intravenously over a one minute period, as suggested by Dr. Grimson.[3] There was an immediate flushing of the face, and the blood pressure dropped from 180/110 to 110/60 mm. of Hg within two

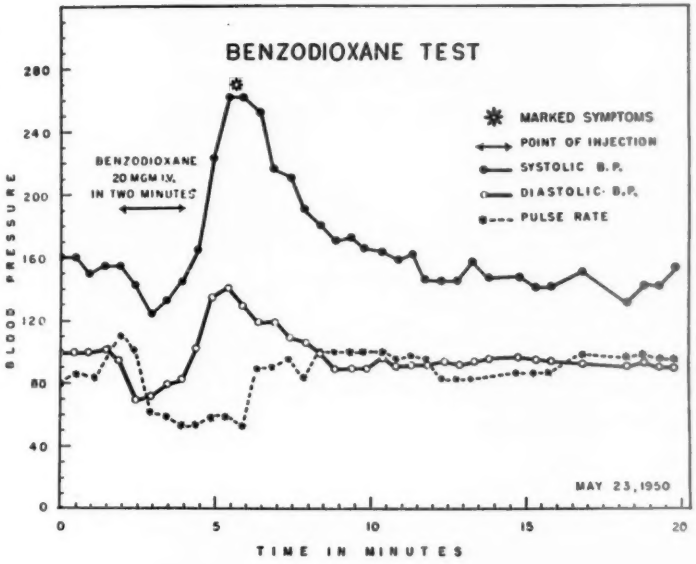

CHART 2.

minutes. The pulse, which had been stable, became irregular and rose from 80 to 164 per minute. Within three minutes the blood pressure rose to 260 +/160 mm. of Hg (chart 3). Again the patient developed marked pallor and a severe throbbing headache. During the hypertension his pulse rate dropped to 70 per minute. During the next 25 minutes his systolic blood pressure spiked above 210 on three occasions.

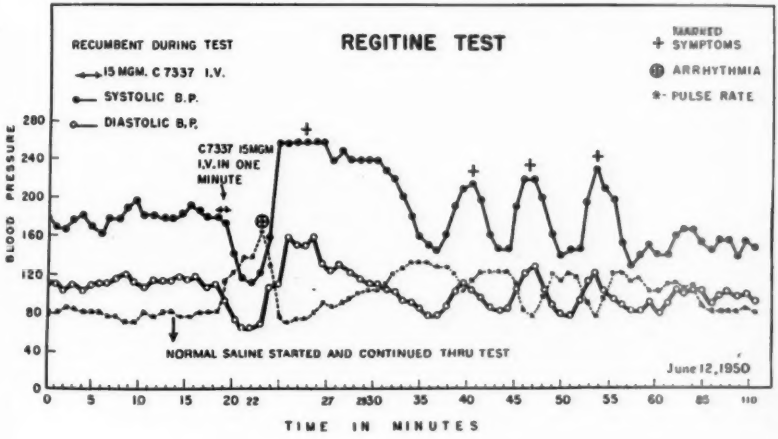

CHART 3.

On June 13 he was explored by our Senior Surgical Consultant, Dr. I. A. Bigger, Professor and Head of the Department of Surgery, Medical College of Virginia, through an upper transverse abdominal incision. A round mass, 6 cm. in diameter, was found above the upper pole of the left kidney. No abnormalities were found in the region of the right adrenal gland. Curiously enough, palpation of the right adrenal gland produced a marked increase of blood pressure. Prior to the removal of the tumor the blood pressure fluctuated widely, ranging from 280/170 to 128/90 mm. of Hg (chart 4). During the ligation of the tumor vessels, moderate hemorrhage was encountered. This was followed by a precipitous fall in blood pressure (80/60 mm. of Hg), which failed to respond to 1,000 c.c. of whole blood given over a period of approximately 15 minutes. An intravenous drip of Neosynephrine

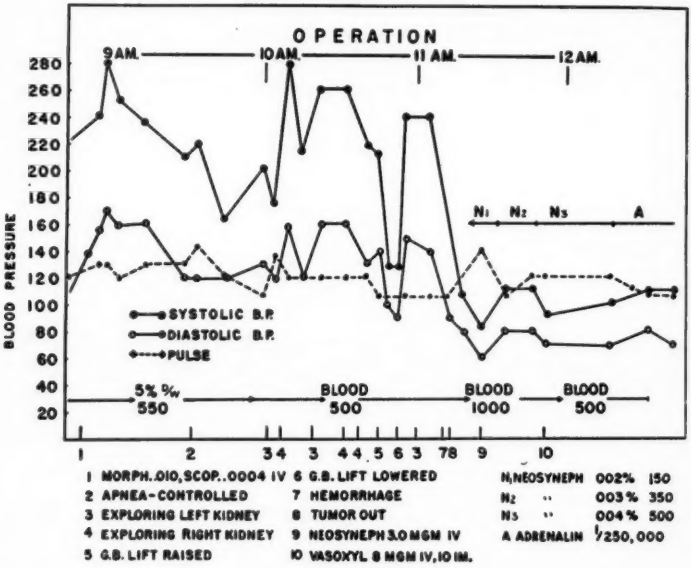

CHART 4.

was started immediately, and it was necessary to give 33.5 mg. in addition to 18 mg. of Vasoxyl during the first hour to maintain satisfactory blood pressure. Neosynephrine was replaced by 1–250,000 solution of epinephrine. In order to decrease the fluid intake, the epinephrine solution soon was changed to 1–100,000 concentration, and the patient received a total of 11 mg. of epinephrine during the first 18 hours postoperatively.

The tumor, which weighed 50 gm., was reported by Dr. Marcel Goldenberg, of Columbia University, to contain .29 mg. of epinephrine per gram and 4.92 mg. of norepinephrine per gram. Microscopic examination revealed a typical pheochromocytoma without evidence of malignancy.

During the first postoperative week the patient's blood pressure varied from 140/90 to 170/125 mm. of Hg. Subsequently it was entirely normal and varied from 120/80 to 130/90 mm. of Hg. The albuminuria disappeared within one week.

The basal metabolic rate was minus 12%. Repeat glucose tolerance test was normal. The electrocardiogram gradually returned to normal over a six month period.

The histamine and the benzodioxane tests were repeated one month following operation, and both tests produced normal blood pressure responses and no symptoms.

Four years have elapsed since operation and the patient has been entirely asymptomatic.

Case 2. A 33 year old white male high school teacher was referred to Richmond Veterans Administration Hospital on June 5, 1952, by Dr. George B. Craddock, of Lynchburg, Virginia, for further evaluation of a probable pheochromocytoma. He had had attacks of intense occipital headaches occurring two or three times yearly during the previous 15 years. The attacks were preceded usually by short periods of anxiety, which progressed to forceful palpitation, a surging sensation in the chest, hyperpnea, numbness and pallor of the hands, tremulousness and severe, pounding occipital headache. The peak of symptoms usually occurred in about five minutes and subsided over a period of 30 minutes. Following the attacks he was quite weak and sweaty. He was unable to provoke or relieve these episodes, and on two occasions had been awakened from sleep by them. During intervals between attacks he felt quite well.

His last episode had occurred two months prior to admission and had lasted several hours. On this occasion his physician noted that his blood pressure was markedly elevated. On previous examinations, when he was asymptomatic, his blood pressure had been normal or only slightly elevated.

During a brief period of observation at another hospital his blood pressure had varied from 100/70 to 180/100 mm. of Hg. The cold pressor test was normal. The histamine test was performed on three occasions; however, a definite hypertensive response was elicited only once. Three hundred milligrams of Etamon (tetraethylammonium chloride), given intravenously, elevated the blood pressure from 155/100 to 240/100 mm. of Hg. Both of these tests produced a mild attack of headache, pallor and sweating. Other laboratory studies were normal.

Physical examination revealed a well developed, well nourished white male in no distress, with a blood pressure of 150/100 mm. of Hg. No other abnormalities were noted.

Complete blood count was normal; serologic test for syphilis, negative; urinalysis revealed a trace of albumin. Fasting blood sugar determinations varied from 120 to 135 mg.%. The glucose tolerance curve was normal. The blood urea nitrogen and serum electrolytes were normal. Basal metabolic rate was minus 16%.

Several electrocardiograms were normal except for a sinus arrhythmia. X-ray examinations of the chest, skull and cervical spine were normal. Intravenous pyelography failed to reveal abnormality of the renal system. Body section radiography of the upper abdomen revealed a diffuse indefinite haziness in the region of the upper pole of the right kidney; a definite mass could not be outlined.

The resting blood pressure varied widely, ranging from 110/80 to 170/120 mm. of Hg, and the pulse varied from 80 to 120. Variations in blood pressure were not always accompanied by symptoms. The cold pressor test produced a rise of 25 mm. of mercury of both systolic and diastolic pressure. No change in blood pressure was noted when deep pressure was applied to the flank regions. The blood pressure responses to changes in body position were insignificant.

The Roth-Kvale provocative test, using 0.05 mg. of histamine base intravenously, produced a fall in blood pressure from 140/95 to 90/60 mm. of Hg within one minute. Within three minutes his blood pressure rose to 240/140 mm. of Hg (chart 5). He had moderate symptoms similar to those of a spontaneous attack during the period of hypertension. Voluntary hyperventilation for six minutes produced a rise in

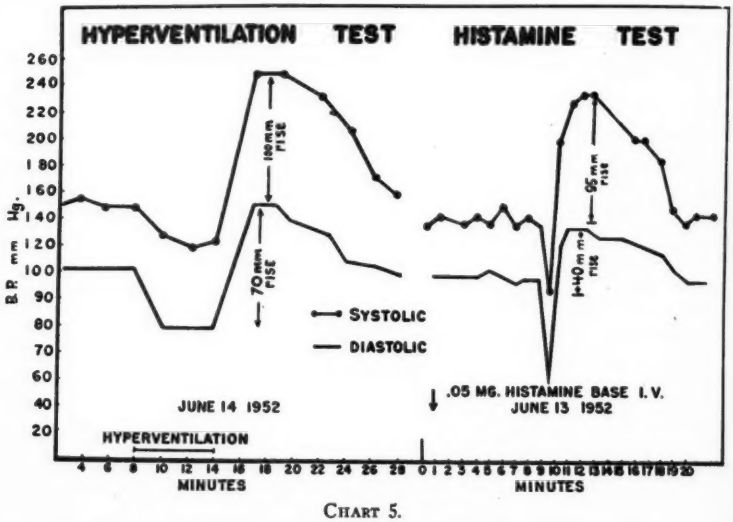

CHART 5.

blood pressure from 160/100 to 250/150 mm. of Hg. This hypertensive episode likewise was accompanied by symptoms. There was a rise in blood pressure from 160/100 to 230/120 mm. of Hg, and mild headache for a period of 10 minutes after he received 0.3 c.c. of 1:1000 epinephrine subcutaneously. He was given 0.2 gm. of sodium amytal at hourly intervals for three doses; however, this did not produce sleep. His blood pressure, taken at one-half hour intervals, dropped slightly during

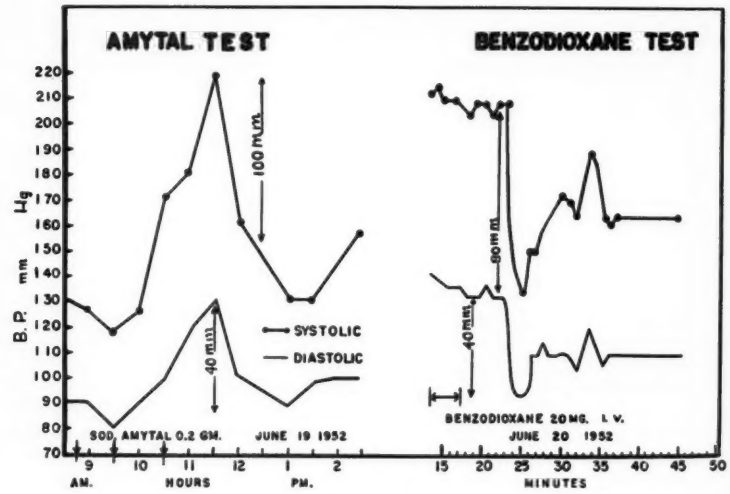

CHART 6.

the first hour and then gradually rose to 220/130 mm. of Hg (chart 6). Slight headache developed during this period.

The benzodioxane test was done when he had a mild headache and his blood pressure was 210/135 mm. of Hg in the recumbent position. He was given 20 mg. of benzodioxane over a three and one-half minute period through the intravenous tube. The blood pressure dropped to 135/95 mm. of Hg (chart 6). He complained of chilliness and profuse sweating.

Five milligrams of Regitine, given intramuscularly when the patient was asymptomatic and the blood pressure was 170/110 mm. of Hg, produced no change over a period of two hours. The blood pressure recordings were made at two to five minute intervals.

On July 8, while the patient was under Pentothal and ether anesthesia, his abdomen was explored through an upper transverse incision by Dr. I. A. Bigger. A tumor weighing 87 gm. was removed from the right adrenal gland. The blood pressure varied widely during the operation, and when the tumor was manipulated it rose to 250/160 mm. of Hg. Small amounts of benzodioxane (1 to 2 mg.) were given intravenously to control severe hypertension. When the tumor was removed his blood pressure fell to 80/60 mm. of Hg. His pressure was maintained at approximately 130/90 mm. of Hg by a frequently regulated drip of 1–100,000 or 1–40,000 norepinephrine solution for the next 72 hours, except for a brief interval when the needle became obstructed. Immediately, his pulse became rapid and thready and his blood pressure unobtainable; however, he responded to re-institution of norepinephrine. Approximately 200 mg. of norepinephrine were given during the first three postoperative days. Except for a minor wound infection, his postoperative recovery was smooth and he was discharged without symptoms three weeks postoperatively.

Microscopic examination of the tumor revealed a pheochromocytoma without evidence of malignant change. Assay of the tumor by Dr. Marcel Goldenberg, of Columbia University, using paper chromatography and a modification of von Euler's colorimetric method, revealed that it contained 4.41 mg. of norepinephrine per gram and 2.94 mg. of epinephrine per gram.

When studied six weeks postoperatively the patient was asymptomatic and his blood pressure was normal on repeated determinations. The histamine, hyperventilation and sodium amytal sedation test were repeated but failed to alter his blood pressure significantly or to induce symptoms. Other laboratory studies were normal. He has been asymptomatic during the two years since the operation.

Discussion

Pheochromocytomas (chromaffin tissue tumors) occur most frequently in the adrenal glands; however, they may occur in the sympathetic chain in the epigastrium, the thorax and even in the cranium. The organ of Zuckerkandl is a fairly frequent extra-adrenal location. Smithwick found a 0.5% incidence of these tumors in patients whose adrenal areas were explored during sympathectomy for hypertension.[3] He collected 270 cases from the literature, of which one third were found at operation and the remaining two thirds at autopsy.[4] MacKeith[5] reviewed 165 cases in 1943 and found 152 adrenal pheochromocytomas (16 of which were bilateral) and 13 paragangliomas. The right adrenal gland seems to be involved about twice as often as the left.[6] Tumors weighing as much as 2,000 gm. have been reported; however, the majority weigh less than 100 gm. Belt and Powell[7] reported a pheochromocytoma which contained 20 mg. of

pressor substances per gram of tumor tissue. (Normal adrenal gland contains 1.0 mg. per gram.) The vast majority of these tumors are benign. McGavack et al.[8] found only eight malignant pheochromocytomas prior to 1942. More recently, Cahill[9] reported that 8% of 139 cases were malignant. The apparent increased incidence of pheochromocytomas in people with neurocutaneous syndromes has been pointed out by several authors recently.[9, 10, 11, 12]

In 1937 Beer, King and Prinzmetal[13] demonstrated a substance in the blood of a patient with a pheochromocytoma which had pharmacologic properties similar to those of epinephrine. Holton[14] in 1949 was the first to identify norepinephrine in addition to epinephrine in chromaffin tumors, and he postulated that norepinephrine might be responsible for attacks of hypertension in patients with pheochromocytoma. Assay studies of these tumors have revealed that they contained from 50 to 90% norepinephrine.[15] U.S.P. standard epinephrine has been reported to contain up to 36% norepinephrine.[15, 16]

Norepinephrine, or Arterenol, is a primary amine identical with epinephrine except for the absence of a methyl group attached to the nitrogen atom. Blaschko[17] and others[18] have done considerable work on the metabolism of pressor amines and have suggested that norepinephrine is a precursor of epinephrine. This certainly seems reasonable, since methylation takes place readily within the body. The exact action of norepinephrine in normal neurohumeral physiology is unknown at this time.

Studies by Goldenberg et al.[19] and West[20] have shown that the cardiovascular responses to epinephrine and norepinephrine are quite different. Goldenberg's observations were made on normal human subjects and subjects with uncomplicated hypertension. Epinephrine intravenously produced a striking increase of cardiac output, a significant rise of systolic blood pressure with little change in diastolic pressure, a slight increase in the mean arterial pressure, a moderate increase of pulse rate, and a sharp decrease in peripheral resistance. Norepinephrine produced no change or a moderate decrease in cardiac output, a significant rise in both systolic and diastolic pressure, a significant rise in mean arterial pressure, a definite decrease of pulse rate and a striking increase in peripheral resistance. A significant rise in pulmonary artery pressure was brought on by both of these substances. Bloomfield et al.[21] reported that the pulmonary artery pressure was normal in people with uncomplicated essential hypertension. When equal amounts of epinephrine and norepinephrine were infused, the effects of epinephrine predominated. Symptoms were more pronounced during epinephrine infusion than during norepinephrine infusions. Norepinephrine apparently has less effect on basal metabolism and glycogenolysis than epinephrine.[6] Apparently the cardiovascular responses of norepinephrine are dependent upon an intact adrenal cortex.

Articles by Smithwick et al.,[4] Aranow,[6] Cahill,[9, 22] Bartels and Arnold,[23] Hatch, Richards and Spiegl,[24] Cahill and Aranow[25] and Shapiro et al.[26]

have emphasized the signs, symptoms and diagnostic tests for pheochromocytomas. If all patients with these tumors had paroxysmal hypertension accompanied by vasomotor manifestations, the diagnosis would be simplified. However, Green [27] reviewed 51 cases and reported that 70% of these had persistent hypertension. Even in this clinically hypertensive group, paroxysmal elevations of blood pressure occur and are accompanied by the same symptoms associated with paroxysms in normotensive individuals. Asymptomatic pheochromocytomas have been discovered during surgery for unrelated reasons. The most frequent symptoms occurring during a paroxysm are forceful palpitation, a surging sensation in the chest, severe headache which is usually pulsating in character, severe anxiety, numbness, pallor and tremulousness of the extremities, nausea and vomiting, dizziness, intolerance to heat, profuse sweating and extreme weakness following attacks. Smithwick [4] reported that excessive sweating occurred in the majority of his cases of pheochromocytoma, irrespective of the type of hypertension. Browne and Meyer [28] reported that 28 of 200 cases of pheochromocytoma reviewed had neurologic complications. Cerebral hemorrhage was the most common complication.

Paroxysmal attacks of hypertension may occur spontaneously or may be induced by change in position, change in temperature, emotional stress, hyperventilation, physical exertion, operative procedures, massage or blows to the abdomen, and by pain. These attacks may last from a few minutes to a few hours or days. A state of shock has been observed to follow prolonged paroxysms.[29-32] Patients with persistent hypertension may be asymptomatic or may have symptoms and signs of advanced hypertensive cardiovascular renal disease. Profound vascular changes have been observed to improve greatly following the removal of a pheochromocytoma.

Hypertension occurring in childhood in the absence of obvious renal disease, coarctation of the aorta or hypertension accompanied by increased basal metabolism, diabetes mellitus or some other endocrine disturbance should make one consider the possibility of a pheochromocytoma. Cahill [9, 22] reported three cases in children in 1948 and was able to find only seven cases reported up to 1951. He emphasized the frequency of multiple tumors in children, and suggested that a further search be made if the blood pressure failed to fall after the removal of one. In 1944, Duncan, Semans and Howard [33] reported a patient whose hypertension and uncontrollable diabetes disappeared after the removal of a pheochromocytoma. Other striking cases of diabetes disappearing after the removal of a tumor have been reported.[34-36] Differentiation from the Kimmelstiel-Wilson's syndrome may be difficult clinically. Several cases of pheochromocytoma have been treated surgically for hyperthyroidism prior to the discovery of the chromaffin tumor.[23, 24] Normal blood cholesterol and protein-bound iodine determinations and normal uptake of I^{131} by the thyroid may be helpful in the differentiation.

Many types of studies have been suggested to establish this diagnosis

since Pincoffs [37] in 1929 reported the first case in which the preoperative diagnosis was made. Roentgenograms, including flat plate of the abdomen, intravenous and retrograde pyelograms, and laminagrams of the kidney areas, have been only occasionally helpful in localizing these tumors. Rarely has calcification within the tumor been noted.[38] Retroperitoneal gas studies may be helpful. Cahill has done a large number of these injections and considers the procedure safe and worth while. Even with considerable experience, he has reported difficulty in interpreting retroperitoneal masses.[25] These tumors have been outlined occasionally by contrast studies of the arterial or venous blood supply.[9]

The intravenous histamine test (.05 mg. of the base) has been used most often to incite paroxysms of hypertension and symptoms. This procedure resulted from the work of Horton and Roth [39] and Roth and Kvale.[40] The pressor response may be due to direct stimulation of the pheochromocytes, or overcompensation by the adrenal medulla (chromaffin tumor) to the initial hypotension produced by the vasodilator action of histamine. This test has been negative occasionally in proved cases of pheochromocytoma and positive in patients in whom a tumor could not be found.[6, 23, 41] It is conceivable that this drug may be dangerous if it produces a marked pressor response, especially in a patient who already has severe hypertension. This can be guarded against by having adrenergic blocking drugs (benzodioxane or Regitine) immediately available. To our knowledge, no fatality has been reported from this test.

Etamon (tetraethylammonium chloride), a ganglionic blocking agent, given in doses of 300 mg. intravenously, has precipitated hypotension followed by an attack of hypertension in cases of pheochromocytomas.[42, 43] Hypertension thus produced can be controlled by having the patient assume an upright position.

Mecholyl bromide was first used to provoke attacks of hypertension in patients with pheochromocytomas by Guarneri and Evans.[44] They suggested that a dose of 25 mg. be given subcutaneously. Serious side reactions have occurred from this dose of drug. Evans et al.[41] have precipitated attacks of hypertension by giving 10 mg. subcutaneously. Mecholyl should be avoided in asthmatics. Adverse reactions can be controlled with atropine. False-positive and false-negative responses have been reported for both Etamon and Mecholyl.[41, 45]

Benzodioxane (2-1-piperidylmethyl-1, 4-benzodioxane), 933F or Benodaine, has been used extensively in attempting to differentiate persistent hypertension due to hyperepinephrinemia from hypertension due to other causes. The exact mode of action of the benzodioxanes and other adrenergic blocking agents is unknown, but it is believed that these substances inhibit the action of epinephrine and similar pressor substances by competition for specific receptors.[46] When given intravenously as outlined by Goldenberg,[2] the drug has a reaction period of 10 to 30 minutes.

Since the introduction of this test in 1947, many authors have reported

false-positive, false-negative and untoward reactions from this drug.[47, 48, 49] Until 1950, Goldenberg [50] had knowledge of false-negative results (no hypotensive response) in only three proved cases of pheochromocytoma. Fifty-nine proved cases of pheochromocytoma had had a definite hypotensive response. He postulated that the false-negative results were due to persistent hypertension from some cause other than hyperepinephrinemia. Several false-positive reactions to benzodioxane (hypotensive response and no tumor found at autopsy or surgery) have been reported during the past five years.[51-53] A false-positive result may be obtained in hypertensives who are receiving sedation during the test period.[54]

Severe hypertensive responses to benzodioxane have been reported.[55, 56] The vast majority of hypertensive patients have a moderate pressor response to this drug.[30, 57] Roth and Kvale [58] and Mason [59] have reported only pressor responses to this drug when it was given to some patients with pheochromocytomas during the normotensive phase. Goldenberg [50] reported a marked pressor response following an initial hypotensive response to benzodioxane. This type of reaction occurred twice in case 1, reported above. This probably resulted from an outpouring of a large amount of pressor amines from the chromaffin tumor in response to the initial hypotension produced by benzodioxane. It has been demonstrated that depressor response of benzodioxane is proportional to circulating epinephrine and norepinephrine.[50, 60, 61]

Regitine, 2-(N,para-tolyl-N M-hydroxylphenol aminomethyl) imidazoline hydrochloride (C7337), another adrenergic blocking agent, has been used to discover pheochromocytomas when surveying large numbers of patients with persistent hypertension.[57, 62] It produces a more prolonged reduction in blood pressure than benzodioxane (30 to 90 minutes), and is given in doses of 5 to 10 mg. intravenously or intramuscularly. False-positive reactions occur more frequently in patients in uremia and those heavily sedated, and when larger doses are used. This drug was studied first by Grimson et al.[63, 64] Grimson has used it to control hypertensive crises which occurred during surgery. A marked pressor response, as noted above in case 1, has not been previously reported to our knowledge.

Dibenamine (N,N-dibenzyl-β-chloroethyl amine) has been investigated extensively by Hecht and Anderson,[65] who were unable to determine its site of action. This drug apparently has an adrenolytic action, since it depresses hypertension produced by infusions of epinephrine and Neosynephrine. The epinephrine reversal has been clearly demonstrated by giving additional epinephrine to one who has received Dibenamine. It has been used also to reduce the severe hypertension of patients with pheochromocytomas during the preoperative preparation.[66, 67] Since its action lasts from 24 to 72 hours, it has been recommended that this drug should not be used for two to three days prior to surgery. On the contrary, Evans et al.[41] and others [68] have used Dibenamine successfully immediately before and during surgery. They have suggested that the hypotensive phase fol-

lowing removal of the tumor is on a cardiac basis, and that preoperative Dibenamine would have prevented it. They do not feel that epinephrine or norepinephrine is indicated. The hypotensive phase following the removal of the tumor in the two cases reported above responded to intravenous epinephrine or norepinephrine. In case 2, it certainly appeared to be life-saving. This has been the experience of other observers.

In case 1 above, it seemed that we were able to produce episodes of hypertension and headache by almost any procedure or test. Paroxysms were produced by sleep, Amytal sedation, orthostatic hypotension, pressure to the right flank and intravenous histamine, benzodioxane and Regitine. Attacks occurring during sleep, during Amytal sedation and after the patient had been standing perfectly still were most likely responses of the tumor to slight reductions of blood pressure, even though these were not recorded. In each instance, blood pressure is normally lowered slightly. The severe attacks of headaches which followed the ingestion of alcohol were possibly precipitated by reduction of blood pressure produced by its vasodilative action, although they may have been due to direct stimulation. Intravenous histamine lowered the blood pressure for a short period prior to the onset of hypertension. Again, hypertension resulted from reduction of blood pressure or from direct stimulation of the tumor, or both. Even though benzodioxane and Regitine were given when blood pressure was only slightly elevated, a definite hypotensive phase preceded the onset of hypertension. Hypertension probably resulted from the outpouring of large amounts of pressor amines which counteracted the adrenolytic action of the drugs. In each test, it appears that the patient's hypertensive responses resulted from stimulation of the tumor by reduction of blood pressure. The mild metabolic disturbances disappeared completely following operation.

In case 2, paroxysms of hypertension and symptoms were produced by hyperventilation, Amytal sedation, intravenous histamine and intravenous tetraethylammonium chloride. The histamine test was done on four occasions; however, a definite hypertensive response was obtained only twice. Benzodioxane given during a period of hypertension reduced the blood pressure to normal. During the amytal sedation test a slight reduction of blood pressure was recorded prior to the onset of hypertension. To our knowledge, no cases have been reported in which paroxysmal hypertension occurred during the Amytal sedation test. Console et al.[68] reported that sodium pentothal precipitated severe hypotension followed by severe hypertension during surgery on a patient with a pheochromocytoma.

Many other tests have been used. Mayock and Rose[69] and others[26, 45] have demonstrated an increased tolerance to epinephrine in patients with pheochromocytoma. This was not demonstrated in case 2, reported above. Pressure or massage to the flank regions will occasionally precipitate an attack of hypertension, but localization of the tumor by this method is unreliable, as noted above in case 1 and reported by Roth and Kvale.[40] Quantitative blood determinations of pressor amine have been done but at

present are impractical. Recent reports of estimation of urinary excretion of pressor amines are encouraging, and this may well develop into the most significant single test.[9, 70, 71]

Surgery on patients with pheochromocytomas should be carefully planned by the internist, surgeon and anesthesiologist. Uncontrollable hypertension during operation has not infrequently caused death.[24] This can be prevented by having benzodioxane or Regitine readily available, or possibly by giving Dibenamine prior to surgery. Dilute solutions of norepinephrine, epinephrine or Neosynephrine should be on hand to control severe hypotension following the removal of a tumor.

Summary

1. Two cases of paroxysmal hypertension and headache produced by a pheochromocytoma have been reported in detail. Unusual responses to various tests and procedures have been demonstrated.

2. A brief review of the general subject of pheochromocytoma has been presented, and difficulty in interpretation of the various pharmacologic tests has been stressed.

3. The common denominator for the production of hypertensive responses in many of the test situations, whether produced by drugs or by other manipulations, appears to be an initial reduction in blood pressure.

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ABERRANT CORONARY ARTERIES: EXPERIENCES IN DIAGNOSIS WITH REPORT OF THREE CASES *

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IN the last few years interest in congenital heart disease has increased inasmuch as surgical treatment is now possible in certain types. An attempt is now usually made to diagnose clinically and to classify anatomically the type of malformation present. Some malformations are difficult to diagnose, requiring such elaborate technics as catherization of the heart chambers and gas analysis of the blood. Many malformations can be correctly diagnosed by ordinary clinical means. Such a malformation is the anomalous origin of the left coronary artery from the pulmonary artery. This condition is very rare and only 54 cases have been so far reported, 34 in infants.[1]

Within three years and in 623 autopsies we have seen three cases of this malformation. This remarkable incidence suggests that this condition is possibly more common than a review of the literature would indicate. Some cases of this nature probably are not published because of the seemingly academic nature of a correct antemortem diagnosis. At the present time the prognosis of the malformation is considered poor.

Review of the literature, and especially of the indispensable classic by Taussig,[2] reveals that this disorder exhibits characteristic clinical manifestations with suggestive radiologic and diagnostic electrocardiographic findings. Thus it should be possible to make the diagnosis during life in many cases. However, correct antemortem diagnosis of this condition is the exception. Our three cases were not diagnosed during life. We suspect that some of these cases are also misdiagnosed at postmortem examination. The incorrect diagnosis of "congenital endocardial fibrosis" or "healed fetal endocarditis with fibrosis" may be made if the misplacement of the origin of the left coronary artery is overlooked.

PATHOLOGY AND PATHOGENESIS

If the origin of the left coronary artery is misplaced and comes off the pulmonary artery, instead of branching from the aorta, the myocardium of the left ventricle is severely affected, as its blood supply consists chiefly of venous blood. This hypoxic state is present only in the left heart and the

* Received for publication July 13, 1954.
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nutrition of the remainder of the body is not interfered with, as it receives blood with normal oxygen content. Thus there is no cyanosis present.

The myocardium undergoes, step by step, the following changes: First there is weakening, with stretching of muscle fibers and dilatation of the ventricle. This is followed by hypertrophy. Then spotted areas of necrobiosis occur which are ultimately replaced by scar tissue that may show small calcifications. This takes place especially in the subendocardial areas and in the papillary muscles of the left ventricle. These degenerative and destructive processes lead to change in size and shape of the heart. The left ventricle greatly dilates and becomes relatively thin and globular. All these changes resemble those seen in slowly developing myocardial ischemia, such as in long-standing coronary insufficiency in adults.

These changes cannot be entirely explained by the reduced oxygen content of the abnormally situated left coronary artery. Many cases of congenital heart disease show oxygen saturation in the arterial blood well below the one in normal venous blood and still no such changes as in this malformation are found. Another causative factor, no doubt, is the low pressure in the aorta.[3] There is a great deal of evidence that at least the destructive changes in the left myocardium occur during the postnatal life and not in the prenatal period, when the pressures in the pulmonary artery and aorta are about the same. Furthermore, most of the symptomatology occurs in this malformation after the second or third month, the time when the ductus arteriosus closes. An open ductus arteriosus increases the pressure in the pulmonary artery, delaying the onset of symptoms. However, venous blood under low pressure in the left coronary artery does not completely explain the profound changes in the left ventricle. No similar changes take place in the heart if the right coronary artery alone originates from the pulmonary artery. Gasul and Loeffler[4] suggest another factor, based on the anatomic position of the coronary arteries. Dilatation and hypertrophy of the left ventricle, which precede the destructive changes, start at the apex and progress toward the base, compressing and finally occluding the branches of the left coronary artery. This leads to fibrosis and more bulging of the left ventricle, and more compression and obliteration of the left coronary arterial branches, causing a vicious circle.

Clinical Manifestations

There is no cyanosis before heart failure sets in. There are no characteristic cardiac murmurs or clubbing of the fingers.

After several asymptomatic postnatal weeks the infant may become a feeding problem. There is frequent display of pain, which at times may be due to true anginal attacks as suggested by the objective evidence of pallor, shock with cold sweat, and occurrence of crying paroxysms after heavy feedings.[5] Later the picture is that of left and often right heart failure.

Diagnosis

Roentgenologic examination shows the heart to be greatly enlarged, due primarily to enlargement of the left ventricle. Upon fluoroscopy, a difference in the force of the contraction of the two ventricles may be seen.

The electrocardiographic findings, according to Bland, White and Garland,[6] are inversion of the T waves in all three leads, combined with low voltage curves and normal axis deviation. Taussig considers this electrocardiogram pathognomonic of this malformation, and definitely differentiating it from many other conditions with great cardiac enlargement and failure without murmurs and cyanosis, such as severe anemia, essential hypertension, coarctation of the aorta, Van Gierke's disease, Fiedler's myocarditis, vitamin deficiencies, acute rheumatic fever, and so-called idiopathic cardiac hypertrophy.[2]

It must be remembered that many cardiac malformations exhibit abnormal electrocardiograms with signs of myocardial ischemia. In addition to the graphs of Bland, White and Garland's [6] case, the electrocardiographic curves of three other cases of anomalous origin of the left coronary artery are published in the literature. In two of these cases the condition was diagnosed during life. While all these curves exhibit signs of myocardial ischemia, such as depressed ST segments and inverted T_1 and T_2, they show different features from Bland, White and Garland's curve. Kaunitz' case [3] exhibits a tendency to left axis deviation, and in serial graphs the T_2 became upright and the ST depression lessened. In Gasul and Loeffler's[4] case, as well as in Eidlow and Mackenzie's [5] case, the graphs do not show low voltage.

Course

In the great majority of cases the condition is fatal during the first year. Approximately 20 cases were found in adults,[7] some even without myocardial fibrosis.[8] Extraordinary anastomosis between the right and left coronary arteries had taken place. Such cases obviously point to the importance of antemortem diagnosis of this malformation. It might be possible to try some type of surgical therapy, such as a Potts-Smith operation, or similar attempts at anastomosis between the aorta and the pulmonary artery, in order to bring more oxygenated blood to the left coronary artery.[4]

Case Reports

Case 1. A three month old female infant died in the hospital with the symptoms of left heart failure and bronchopneumonia.

The prenatal course of the infant had been uneventful, the delivery normal. Two siblings were living and well. The infant weighed seven pounds two ounces at birth and eight pounds at death.

The history was that of a feeding problem during the first two months, with colics, diarrhea and vomiting. On December 3, 1948, the baby was admitted to the hospital with fever of three days' duration, and dyspnea. Physical findings were

râles in the lungs and diminished breath sounds in the left axillary region. The diagnosis of malnutrition and upper respiratory infection was made, and the baby was treated accordingly. Laboratory examinations showed a normal urine, a red blood cell count of 3,200,000, with 66% hemoglobin, 6,000 white blood cells, with a normal differential count. An x-ray picture of the chest was reported as follows: "The domes of the diaphragm are normal. The lung fields are clear. There is a distinct enlargement of the heart which almost fills the left side of the chest. Mediastinum and the aorta are believed to be normal. . . . Impression: Congenital heart disease; probably this

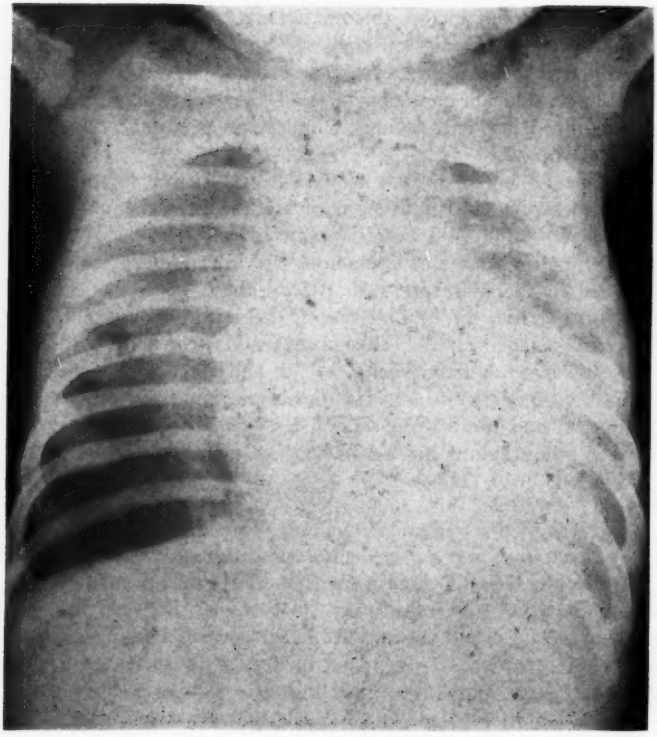

FIG. 1. X-ray of chest showing enlarged heart and pneumonitis.

represents a right-sided enlargement, which in the absence of pulmonary congestion and with the history of cyanosis would be most likely suggestive of stenosis of the pulmonary valve."

After this report was received by the clinician a pointed note was made on the chart that there were no attacks of cyanosis. After five days in the hospital the baby was dismissed afebrile. In the diagnosis on dismissal the pediatrician also considered enlarged thymus.

On December 28, 1948, the baby was re-admitted to the hospital. Between the admissions the baby did not do well: she had respiratory difficulty and loose stools, and lost weight. On admission the infant had a temperature of 100.2° F. and signs

of consolidation over the right upper lobe. Another chest x-ray picture (figure 1) showed an enlarged heart. At this time it was considered to be enlarged on the left side. There was also consolidation in the right lung. The working diagnosis was made of congenital heart disease without valvular involvement and pneumonitis. Further studies could not be carried out as the baby died suddenly.

Postmortem examination of the malnourished infant revealed generalized passive congestion of the parenchymatous organs. The right lung showed confluent bronchopneumonia.

The heart (figures 2 and 3) was greatly enlarged, measuring about 7 cm. at the base and weighing 88 gm. (Normal average weight for this age, 23 gm.) The heart was globular, with a rounded apex. The left ventricle measured 0.5 cm. in thickness and the right ventricle about the same. The trabeculae carneae and papillary muscles

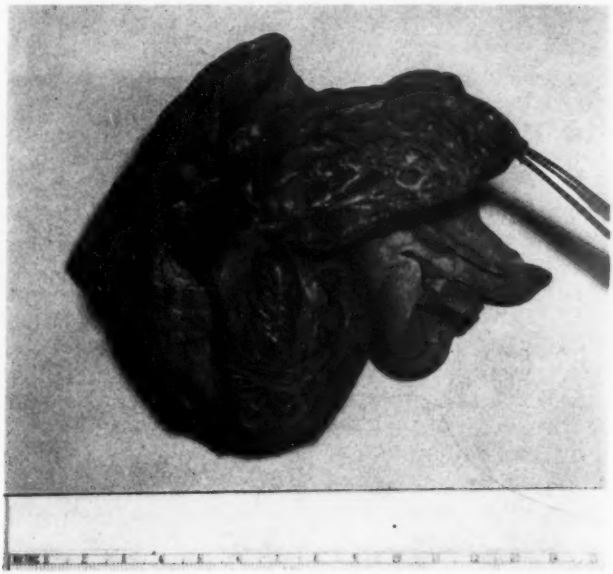

FIG. 2. View of left ventricle showing hypertrophy, dilatation and subendocardial fibrosis.

of the left chamber were flattened. The endocardium of the left ventricle was thickened with white discoloration. The valves were delicate. The right coronary artery originated from the aorta, while the left coronary artery showed the ostium in the left cusp of the pulmonary artery. From here it divided after a short (0.7 cm.) trunk in the normal fashion into a descending ramus and into a left circumflex artery. The foramen ovale was closed. The aorta showed a narrowing to about one-half its diameter beneath the origin of the left subclavian artery. The ductus arteriosus was closed.

Microscopically, the left myocardium showed streaks of fibrous tissue with hyalin and only a few cellular elements. This tissue was accumulated beneath the endocardium. The remaining muscle fibers were slightly thickened with irregular nuclei. Occasionally a small branch of the coronary artery was encountered which showed narrowing of the lumen by proliferated intima, as seen in Kaunitz' cases.[3]

Discussion: This case exhibited the usual history for this malformation; however, because of omission of electrocardiographic examination and misinterpretation of the x-ray picture, a diagnosis was not made during life.

The electrocardiogram might have given the decisive clue. It is doubtful of course whether each such case shows a tracing identical with that described in the case of Bland, White and Garland;[6] however, the electro-

FIG. 3. View of right ventricle and opened pulmonary artery. Arrow points to ostium of left coronary artery.

cardiographic signs of constant severe myocardial ischemia would be helpful. This case stimulated great interest in electrocardiography of infants among the local pediatricians. (Unfortunately, for obvious reasons related later, this examination could not be carried out in the two other cases of coronary displacement seen by us.)

Misinterpretation of the x-ray findings in this case is explained as follows: It is very difficult for the radiologist to determine which side of the heart is enlarged without many pictures and fluoroscopic examinations.

Pictures which might decide this issue must be taken in an oblique position, and it is often impossible to keep a sick, resisting infant in such a position. The same is true of fluoroscopy in estimating pulsation difference of the ventricles. In this particular case, the radiologist did not receive an adequate history; the baby was never cyanotic. If forced to make a definite diagnosis, a radiologist considers the most frequent possibility, and the majority of congenital heart malformations do show right-sided enlargement.

The malformation was not correctly diagnosed even at the autopsy table. The incomplete aortic coarctation was thought to be the cause of the left cardiac hypertrophy and terminal dilatation. The coronary arteries were not inspected on the first examination; however, in reviewing the case the consultant in cardiology (one of us, W. C. S.) brought out the fact that death due to incomplete coarctation of the aorta rarely occurs in infancy. It was the cardiologist who suggested the possibility of a misplaced left coronary artery, and this was promptly found upon reëxamination of the gross specimen. The pathologist (one of us, S. W.) was at that time not familiar with the existence of such a malformation and was not accustomed to give much attention to the coronary arteries of infants or newborn. This inexactitude seems to be not uncommon among pathologists. In many reports of cardiac malformations the coronary arteries are not even mentioned. In a recent article on endocardial sclerosis [9] (a condition in which the cardiac pathology is very similar to that seen in anomalous origin of the left coronary artery), the coronary arteries were noted in only two of six cases. This does not imply that these four cases were due to abnormal coronary arteries, or that the authors did not examine the coronary arteries in these cases. It is mentioned only because where it is of differential diagnostic importance, coronary arteries in the infantile heart have been given less attention than those in the adult heart. Such an attitude radically changes after such a personal experience as was afforded by the previous case, and the alertness acquired helped to diagnose the two subsequent cases.

Case 2. A six month old female infant died suddenly March 22, 1950, at home in her carriage. Death was preceded by a spell of violent crying, accompanied by extreme pallor. A pediatrician who was summoned declared the baby dead and obtained permission for autopsy.

The baby had expert pediatric postnatal care. At no time was there any clinical evidence that anything was wrong.

Autopsy revealed a very well developed infant weighing 17 pounds. Pertinent pathology was found only in the heart (figures 4 and 5), which was greatly enlarged, weighing 112 gm. (Average normal for this age, 31 gm.) The apex was quite rounded. The diameter at the base was nearly 9 cm. The left ventricle measured up to 0.8 cm. and showed white strands in the muscle, which collected to a nearly solid white, opaque sheet beneath the endocardium of the anterior inferior portion of the left ventricle and the adjoining septum. The left coronary artery originated in the middle of the left cusp of the pulmonary artery. The right ventricle measured about 0.3 cm. The right coronary artery originated from the aorta. The valves were delicate. The ductus arteriosus and the foramen ovale were closed.

Microscopic sections of the left ventricle showed the characteristic fibrosis between thickened muscle fibers, with hyalinization and spotted areas of calcification, especially near the apex. The left arterial branches did not exhibit endarteritic narrowing of the lumina; the venous sinuses, however, seemed to be enlarged.

Discussion: This baby obviously died with the clinical features of a sudden, unexpected and fatal heart attack. Since there had been no previous symptoms, one can only speculate as to how the case could have been diagnosed. Chest x-ray as a part of postnatal examinations (even in the absence of suggestive symptoms) would have revealed the enlarged heart, and then electrocardiographic study would have suggested the diagnosis. If the antemortem diagnosis had been made, the remarkably excellent nutritional and developmental state of this baby would have suggested a trial of surgical treatment.

Misplacement of the coronary artery ostium may take place if the aortic bulb septum which divides aorta and pulmonary artery deviates in embryologic life so as to include one or even both coronary arterial ostia in the pulmonary artery. What causes this septum or, for that matter, any other

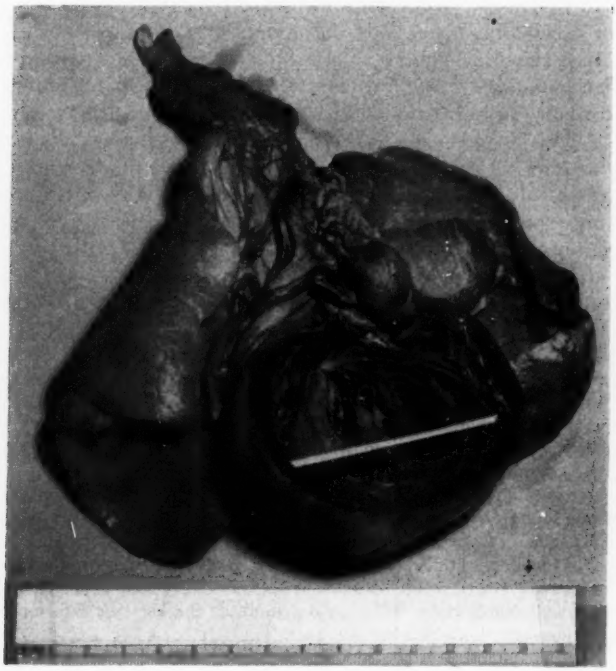

FIG. 4. Opened globular left ventricle displaying the hypertrophy and dilatation with subendocardial fibrosis.

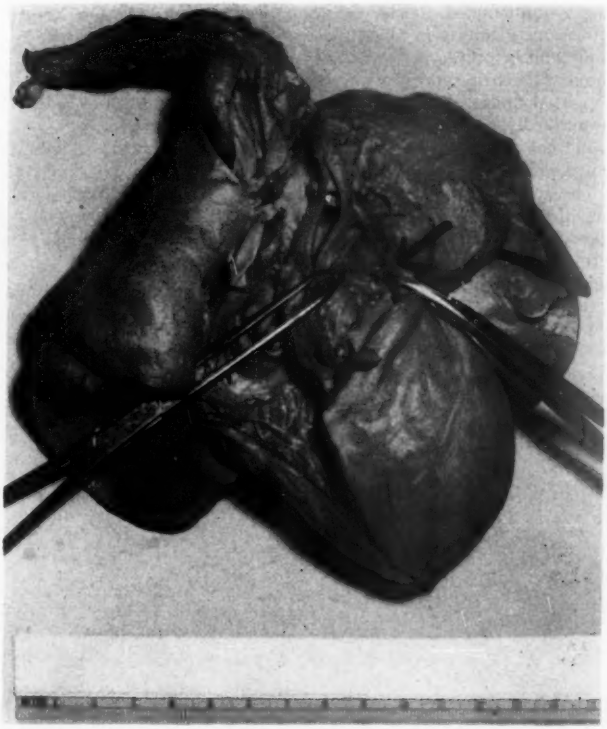

FIG. 5. Arrow points to left coronary origin in pulmonary artery.

septum in the heart to deviate, with resulting malformation, is still not known.

Case 3. A 22 year old primipara was admitted in active labor on November 3, 1951. Her pregnancy had been followed by an obstetrician and had not been unusual. Pelvic measurements were adequate, weight gain had been 20 pounds, and laboratory work was within normal limits (except for a basal metabolic rate of minus 14, for which she received 1 to 1.5 gr. thyroid daily). On admission her physical examination was within normal limits for term pregnancy. The blood pressure was 122/88 mm. of Hg. The fetal heart rate was 132 per minute. Labor was not remarkable, and she delivered a living male under chloroform anesthesia after episiotomy and low forceps were applied. Her postpartum course was uneventful.

The baby weighed eight pounds four and one-half ounces and appeared grossly normal at birth, although he cried poorly for 10 minutes. Thereafter stimulation was necessary to elicit a cry. The baby became moderately cyanotic and dyspneic, increasingly so with exercise. He was placed in an incubator with oxygen, where he remained cyanotic and lethargic. On November 4 examination by a pediatrician did not reveal signs of intracranial hemorrhage. The lungs were described as clear and the heart was not remarkable on auscultation. When out of oxygen or when

oral feeding was attempted, the baby became deeply cyanosed. On November 5, the respiration became grunting in type. Secondary atelectasis was suspected. The baby died suddenly and before an order for x-ray of the chest was completed.

At autopsy the baby appeared well developed, measuring 56 cm. in length and weighing eight pounds. The skin was definitely cyanotic. All parenchymatous organs were markedly congested, and there was some free fluid in the serous cavities. The lungs did not show atelectasis but were markedly edematous. The heart (figures 6 and 7) was enlarged and weighed 56 gm. (Normal average weight in newborn, 17 gm.) The apex was somewhat rounded. The left ventricle was enlarged and the myocardium thickened to 0.5 cm. The pericardium and endocardium appeared hazy. The myocardium had a peculiar red-tan appearance and was extremely friable. The valves were delicate. Foramen ovale and ductus arteriosus were open. Both coronary arteries originated from the pulmonary artery; the right coronary arterial ostium was placed in the middle of the posterior cusp behind the valve leaf, and the ostium of the left coronary artery in the left cusp near the left upper attachment of the leaf.

Microscopic sections did not show fibrosis of the myocardium. The muscle fibers of each ventricle were somewhat thickened with irregular nuclei. There were faint vacuoles in the fibers, especially beneath the endocardium, and on frozen section stained with Sudan III they proved to be fat droplets.

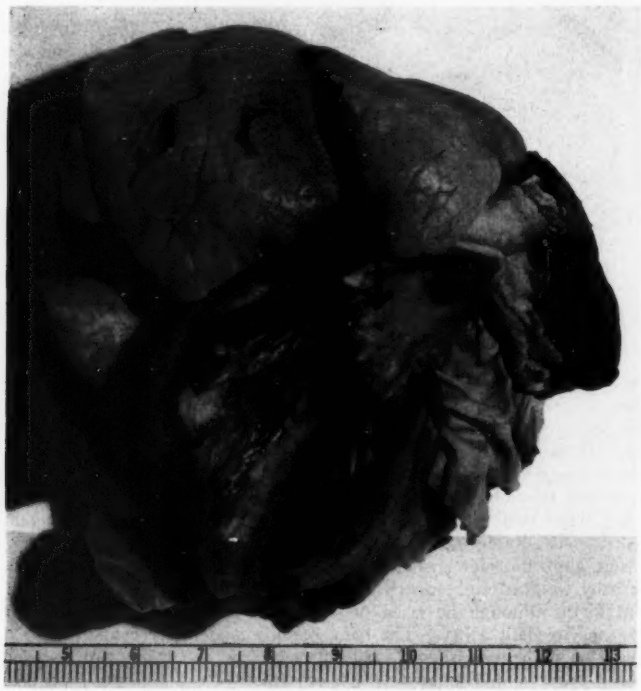

FIG. 6. Opened right ventricle and pulmonary artery. The semilunar valves are dissected off, showing the opening of right and left coronary arteries (arrows).

FIG. 7. Left ventricle, septum and aorta. The aortic valve leaves are dissected off to show absence of coronary ostia.

Discussion: In this case both coronary arteries originated in the pulmonary artery. Obviously this malformation is not compatible with life beyond a few days. Only two such cases are on record, one living for a few hours only,[10] the other for 10 days.[11] The cyanosis in our case is to be explained by the heart failure rather than by the malformation per se. Other signs of right- and left-sided heart failure were found. The hypertrophy of the heart in our case was considerable, since it was more than three times heavier than the normal average. This must have developed during prenatal life. It is likely that at least part of the morphologic changes in the heart take place before birth.

SUMMARY AND CONCLUSIONS

Three autopsied cases of anomalous origin of the left coronary artery have been described; two infant girls and one infant boy died at the ages of three months, six months and two days, respectively. Associated malformations were found in two of the cases. In one case the right coronary artery also originated from the pulmonary artery, and in the other case

there was moderate aortic coarctation. Possibilities of clinical diagnosis were discussed. X-ray of the chest as part of postnatal care and with electrocardiographic study in all cases showing cardiac enlargement is advised.

After study and experience in diagnosing our three cases, we are convinced that the presence of anomalous origin of the coronary arteries is overlooked more often than suspected. Since the patient may be entirely asymptomatic until sudden death, the true incidence of this malformation will be known only when a larger study has been made which includes chest x-ray on all infants at some point during the first two months of life.

Not only is the correct antemortem diagnosis of academic value and of value in preparing the parents of a sick child for a possible sudden ending, but also a goodly number of these cases reach adult life and, if diagnosed, could stimulate methods of surgical correction in selected cases. Surgery for this malformation at the present time is considered of doubtful value by Maloney and Blalock,[12] but suitable methods may be developed in the future.

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CHRONIC AURICULAR FLUTTER*

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AURICULAR flutter is an arrhythmia well known as an electrocardiographic entity. It is most often discovered upon study of patients with very rapid heart action, especially in rheumatic cardiacs and thyrocardiacs, and in patients with recent myocardial infarction. The electrocardiographic characteristics and the physiologic features of auricular flutter are described in all general medical texts,[1] but the clinical features are only briefly referred to even in the cardiology texts.[3] It is generally indicated, particularly in the American literature, that flutter lies between auricular tachycardia and auricular fibrillation in duration, incidence of organic heart disease, and rapidity of auricular rate. Friedberg,[3d] for example, points out that flutter has a greater tendency than auricular tachycardia to persist, but he refers to cases of long standing as rarities in the literature. In a similar vein, White [3b] states that auricular flutter lasts for minutes, days, or weeks, but rarely for months or years. He, too, refers to several patients with flutter of many years' duration as unusual cases in the literature. Lewis, on the other hand, indicated as far back as 1912 in his first article on flutter,[2a] and again in his textbook published in 1933, that auricular flutter, like fibrillation, tends to persist.

Since in the past few years we have had the opportunity to study seven cases of persistent or established flutter, we have been impressed by the relative paucity of information available on the course and clinical problems of auricular flutter. We therefore felt it would be of interest to report our cases with emphasis on the clinical problems of diagnosis, complications and treatment.

INCIDENCE

All cases of auricular flutter (acute and chronic) constitute only a small percentage of the arrhythmias seen in clinical medicine. Prinzmetal introduces his recent publication [5] on auricular flutter with the statement that "auricular flutter is a relatively rare cardiac disorder." Bell [4b] reports finding only 52 cases in 10 years among 13,000 electrocardiograms. On the other hand, White [3b] reports diagnosing auricular flutter about one twenty-fifth as frequently as auricular fibrillation by clinical means, and as much as one fourteenth as frequently by the electrocardiogram. Our own experience has been that, while electrocardiograms with auricular flutter are by no means rare, they are seen in the proportion of only about 1:50 compared with auricular fibrillation.

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The incidence of chronic flutter cannot be estimated because there have been no studies on this subject. The occurrence of cases of persistent or established flutter is referred to but not elaborated upon in articles on paroxysmal auricular flutter. Articles on chronic flutter have been limited to individual case reports.[2] Even the cardiologic texts [3] give no information other than what is contained in these reports.

Our series of seven cases gathered within a few years suggests that the condition is more frequent than one might gather from the literature. One reason for this may be the fact that the condition is more often missed than recognized, as is discussed under "Diagnosis" (unless a so-called auricular lead is used for the electrocardiographic examination).

Etiology

Approximately 90% of the cases of auricular flutter are associated with organic heart disease.[4b, 4c] This compares with an organic heart disease incidence of 95% in auricular fibrillation, and 50% in paroxysmal auricular tachycardia. The cardiac conditions most frequently found are hypertensive arteriosclerotic heart disease (40%) and rheumatic heart disease (30%). Thyrotoxicosis is reported in about 3%. Approximately 20% of the cases reported have shown enlarged hearts for which no specific etiology was identified.

In only one of the five large series of auricular flutter in the literature is there a breakdown on the causes of persistent flutter. Hermann and Hejtmancik [4a] report a series of 82 cases of auricular flutter. Defining established flutter as cases persisting over 72 hours, they list 50 as established flutter. Sixty-two per cent of those with established flutter were due to arteriosclerotic heart disease, 16% to rheumatic heart disease, 6% to thyrotoxicosis, 10% miscellaneous * and 6% were without organic heart disease. In the total group of 82 cases approximately 65% showed evidence of arteriosclerotic heart disease, 10% rheumatic heart disease, 14% thyrotoxic and miscellaneous forms of heart disease and 9% no evidence of organic heart disease. The examples of persistent flutter published as individual case reports have all been presented as having no organic heart disease.[2] None of the cases was autopsied.

Clinical

On physical examination there are no pathognomonic findings in auricular flutter. A rapid, regular ventricular rate of 160 to 180 is characteristic of flutter but does not differentiate it from auricular, nodal or even ventricular tachycardia. A phlebogram (jugular pulse tracing) may demonstrate multiple oscillations of the "a" (auricular) wave for each ventricular beat,[3] but often this cannot be distinguished even on the most careful inspection of neck vein pulsations. Pressure exerted over the carotid sinus,

* "Miscellaneous" includes syphilitic heart disease, neoplastic and constrictive pericarditis.

on the other hand, can provide cogent support for the diagnosis of auricular flutter. At times carotid sinus pressure has no effect; at other times, however, carotid sinus stimulation may temporarily decrease the ventricular rate by a fraction, such as one-half or one quarter; at times by odd multiples —two-thirds, four-fifths, etc., corresponding to the extent of AV block induced by this procedure. Often carotid sinus pressure produces asystole of variable duration. These effects are transient, and with release of pressure the ventricular rate ordinarily returns to its original level. The production of transient slowing in auricular flutter is in contrast to the effect of carotid sinus pressure in auricular tachycardia, where there is either dramatic cessation of the arrhythmia or no effect whatever, and in ventricular tachycardia, where there is no effect, even temporarily. In many cases of auricular flutter the heart action is totally irregular, simulating auricular fibrillation, because of varying AV block. In these cases auricular flutter is detected only by the electrocardiogram, and even here with difficulty (as is discussed under "Electrocardiography").

One other auscultatory finding may often be detected in cases of auricular flutter. In cases with varying degrees of AV block the first heart sound will be found to vary in intensity. Levine has correlated the intensity of the first sound with the duration of the PR interval, demonstrating by phonocardiograms that when the PR interval increases over 0.20, the first sound becomes diminished in intensity. In addition, the relationship between PR and intensity of the first heart sound is influenced by the ventricular rate. Thus the PR at which the loudest first heart sound occurs will differ for slow and rapid heart rates. Variation of the intensity of the first heart sound has been recognized as a feature of complete heart block, identified by the so-called *bruit de canon.* In 1949 Harvey and Levine [6] reported the frequent occurrence of the same phenomenon in most cases of auricular flutter.

Diagnosis

Although the diagnosis of auricular flutter can be suspected, the final arbiter is the electrocardiogram. The characteristic electrocardiographic findings are:

1. Absolute regularity of the auricular (F) waves.
2. Demonstration in any one lead that the iso-electric period does not exceed 0.04 second.
3. Atrial rate of 200 to 360 (as compared with a rate of 160 to 240 in paroxysmal auricular tachycardia). Ventricular rate usually a fraction of the atrial, most commonly one-half or one quarter, occasionally equal in rate to the atrial, and rarely as little as one sixth as rapid (except in cases with complete heart block, where the ventricular rate may be only one tenth of the auricular rate).
4. "F" or flutter waves, which represent auricular activity. These often have a typical configuration in one or more leads, described as saw tooth.

In most cases of auricular flutter one will have little difficulty in recognizing these diagnostic features. In a number of cases, however, auricular flutter masquerades as flutter fibrillation (case S. K.), and less often as paroxysmal auricular tachycardia. Some of these cases are uncovered by means of a so-called auricular lead, recorded by application of the precordial electrode to the right of the sternum somewhere between the first and fourth intercostal spaces, from which point the auricular activity may be recorded most directly. In some cases this lead will bring out flutter waves not detectable in the conventional leads.[7] This is well shown in our first patient. Some authors[8] have shown that with the conventional precordial positions the CR leads will show auricular activity more clearly than will the CF or even the V leads.

In some cases the diagnosis of auricular flutter can be established only by an esophageal electrocardiogram, which most accurately reveals auricular activity.[9]

Treatment

The first objective in patients with auricular flutter is to reduce the ventricular rate so that the myocardium may function efficiently. This can be accomplished rapidly by digitalis in almost all cases. By its action on the AV node digitalis can increase AV block and prevent the rapidly discharging auricles from stimulating the ventricles to more than 60 to 90 beats per minute.

The second objective in treatment is the restoration of regular sinus rhythm. In 50 to 60%[4a,4d,10] of the cases digitalis will restore regular sinus rhythm, but even when it fails to revert the rhythm digitalis will be of great benefit by slowing the ventricular rate. Quinidine, on the other hand, will slow the rate only when it succeeds in converting the rhythm to regular sinus rhythm. This evidently occurs because the effect of quinidine on the auricle (increasing refractory period more than conduction time) is greater than its action on the AV node. If quinidine prolongs conduction time more than it increases the refractory period it may cause acceleration of the ventricular rate by reducing the auricular rate to one at which the ventricle can respond at each stimulation. Because of the possibility that digitalis will slow the ventricular rate even if it does not restore regular sinus rhythm, while quinidine will not slow and may even speed the ventricular rate if it fails to induce sinus rhythm, most workers[10] prefer to digitalize the patient with flutter, and use quinidine only if digitalis has failed to alter the rhythm. A few cases fail to revert to regular sinus rhythm after digitalis and quinidine. These constitute a considerable portion of the cases of chronic flutter.

Complications

1. *Thrombo-embolism:* The incidence of thrombo-embolism in patients with flutter cannot be estimated accurately, since most cases are paroxysmal

in nature. Nevertheless, it can be stated that the incidence must be slight compared with thrombo-embolism in auricular fibrillation because the vast majority of systemic embolizations in rheumatic cardiacs occur in known chronic fibrillators.[13]

The incidence in patients with chronic flutter is unknown. It might be anticipated that the danger is not insignificant, since there is practically no auricular ejection in auricular flutter and therefore stasis results, as in auricular fibrillation. Therefore, in chronic flutter, especially when associated with organic heart disease, the danger may approach that of chronic auricular fibrillation. In our small series three patients died suddenly. Autopsy performed on the third patient revealed no auricular thrombus. Prior to this examination it was thought that the other two deaths were probably embolic.

Because of the hazard of thrombo-embolism in auricular fibrillation, Askey,[11] Levine [12] and Sokolow [13] have urged conversion of all fibrillators to regular sinus rhythm.

Case Reports

Case 1. S. K., a 58 year old housewife, was re-admitted to the Beth-El Hospital on November 28, 1948, from the cardiac clinic because of dyspnea and tachycardia.

The patient had first been admitted to the hospital on February 19, 1946, because of a thrombophlebitis. Examination at that time also revealed signs of mitral stenosis and insufficiency. After four weeks the patient was discharged to the peripheral vascular clinic, which she attended for two months. She was then transferred to the cardiac clinic because of palpitations and exertional dyspnea. An electrocardiogram was reported to show auricular fibrillation. The patient was given digitalis and quinidine, but her symptoms and electrocardiographic findings persisted.

Nine weeks prior to the second admission to Beth-El Hospital the patient was admitted to another hospital in congestive heart failure. This responded to treatment. She was also given quinidine and had an unexplained episode of coma, from which she recovered without sequelae. She was then discharged to the clinic and was subsequently seen in the Beth-El Hospital cardiac clinic and hospitalized.

On physical examination the patient was in moderate respiratory distress. The neck veins were not distended; the vascular pulsations in the neck were synchronous with the heart beat at a regular rate of 188. The heart appeared enlarged. Venous pressure was 88 mm., with no change on liver pressure. Calcium gluconate circulation time was 30 seconds, ether time 9. Electrocardiogram showed a rapid, regular, supraventricular tachycardia. Subsequently a special auricular lead in the third right intercostal space revealed auricular flutter. On the day of admission the patient received 1.2 mg. digitoxin, with slowing of the ventricular rate to 90, but electrocardiographic evidence of flutter persisted.

During the remainder of the patient's stay in the hospital the ventricular rate ranged from 40 to 120. The rhythm was at times perfectly regular, at others occasionally irregular, and at times grossly irregular. The auricular lead already referred to identified these changes as representing auricular flutter with varying block. At one point, when it was felt the patient was fibrillating, digitalis was stopped and regular rhythm resulted, but this was merely auricular flutter with constant block. At another point the ventricular rate was reduced to 38 but the flutter was not interrupted.

The patient was finally discharged to the clinic. After discharge she sustained a cerebrovascular accident and died.

Summary: This patient is known in retrospect to have had auricular flutter for at least two and one-half years. She had organic heart disease, rheumatic in origin, with mitral stenosis and mitral insufficiency. Her course was characterized by bouts of congestive failure and two cerebral episodes, presumably embolic.

It is of interest that several efforts to convert the arrhythmia with digitalis and quinidine failed.

Comment: This patient's course was similar to that of the chronic rheumatic with mitral stenosis who develops congestive failure with auricular fibrillation. In this case chronic flutter was attended by the same fatal outcome.

The electrocardiograms in this case (reported in detail by Appleman et al.[7]) graphically illustrate how a case of auricular flutter may masquerade

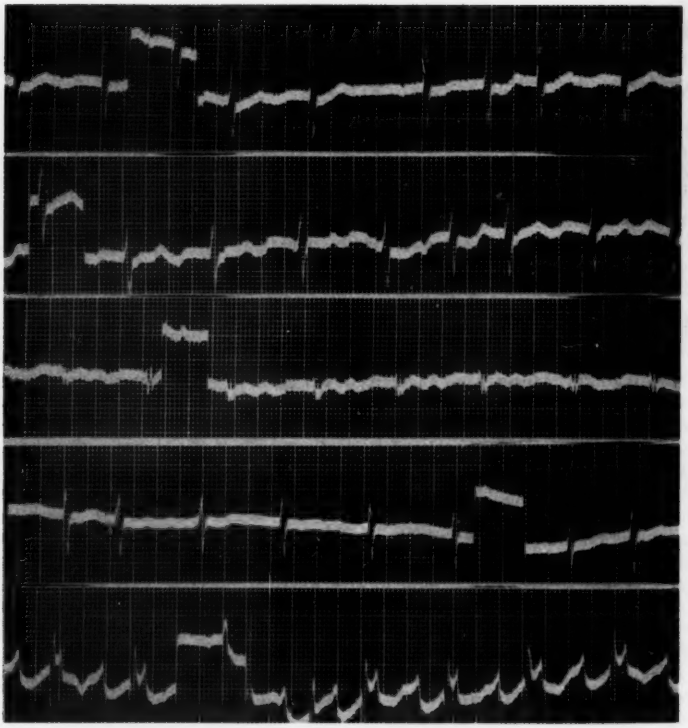

FIG. 1. S. K. Electrocardiogram appears in conventional leads to show auricular fibrillation with no definable P waves and irregular ventricular activity. "Auricular lead" shows sawtoothed auricular flutter waves at a rate of approximately 180 and an irregular ventricular response. Further confirmation of this interpretation of auricular flutter is found in figure 2 (showing regular 2:1 response of the ventricles) as well as in other electrocardiograms, not shown, in which the tracings simulate nodal bradycardia and supraventricular tachycardia with the same underlying auricular activity but varying ventricular response. The lowest tracing is the "auricular lead."

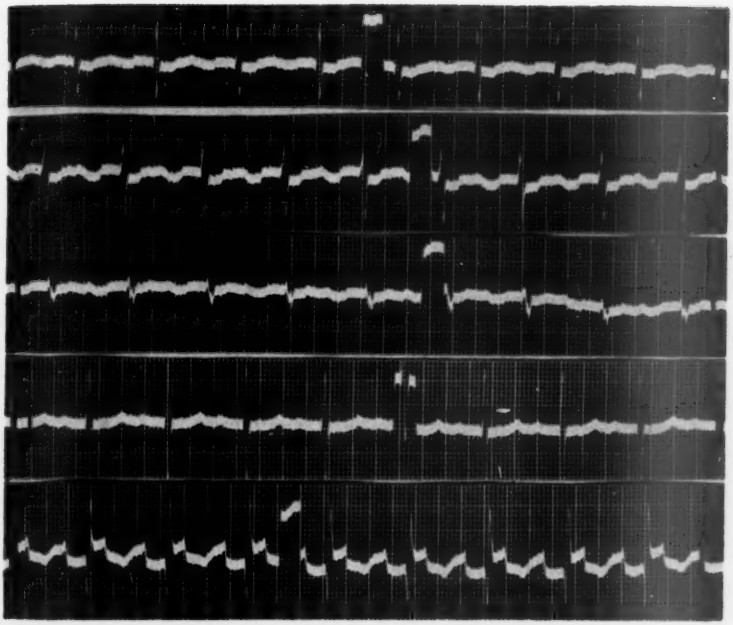

FIG. 2. S. K. Conventional leads (and auscultation) indicate regular sinus rhythm but "auricular lead" uncovers persistent auricular flutter mechanism, auricular rate 180, ventricular rate 90. The lowest tracing is the "auricular lead."

as auricular tachycardia, auricular fibrillation, or nodal and/or regular sinus rhythm with conventional electrocardiograms. Only the so-called auricular lead uncovered flutter in this patient both when the rhythm was grossly irregular, simulating auricular fibrillation (figure 1), and when regular, simulating conversion to regular sinus rhythm (figure 2). There is no way of estimating how many cases of chronic auricular flutter are masquerading in this fashion as cases of chronic auricular fibrillation, but we suspect they are more frequent than is generally conceded.

Case 2. A. B., a 58 year old housewife, was admitted to Beth-El Hospital on December 21, 1951, because of recurrent epigastric pain. Five months, then four weeks and again one day prior to admission the patient had experienced attacks of epigastric pain, with chills and a temperature of 103° F., and just prior to admission accompanied by palpitations, nausea and vomiting.

On physical examination the patient did not appear acutely ill. Blood pressure was 130/66 mm. of Hg; the ventricular rate was 120. The remainder of the examination was negative. The initial impression was that of cholecystitis and psychoneurosis.

An electrocardiogram on admission revealed auricular flutter, with an auricular rate of 300, a ventricular rate of 150 and ST depressions. X-ray of the chest revealed left ventricular enlargement and calcification of the aorta.

Course: Quinidine was prescribed initially but the patient was unable to tolerate the drug because of vomiting. Digitoxin was then given, 0.6 mg. stat and 0.2 mg. every four hours for three doses. The next day the auricular rate was 280 and the ventricular rate was 140. In the next week the patient received 0.2 mg. daily, with occasional supplements. Auricular flutter persisted and the auricular rate remained 300, while the AV block increased and the ventricular rate fell to 75. The patient was then discharged on maintenance digitalis.

Comment: This patient's course is familiar to cardiologists. Most authors describe satisfactory control of the ventricular rate by digitalis in patients whose auricular flutter is not reverted to regular sinus rhythm by quinidine. Presumably this should be as satisfactory in chronic auricular flutter as it is in chronic auricular fibrillation when the ventricular rate is controlled by digitalis.

Case 3. D. W., a 72 year old male, was seen in the Beth-El Hospital cardiac clinic on January 20, 1950, because of hypertension.

Physical examination revealed a blood pressure of 210/110 mm. of Hg, an enlarged heart, basal râles and peripheral edema. X-ray revealed moderate chronic passive congestion and an enlarged heart. The electrocardiogram showed auricular flutter, with an auricular rate of 200, a ventricular rate of 100, T_1 flat and TCF_4 diphasic.

Course: The patient was digitalized slowly (1.5 grains four times daily for four days, and then 1.5 grains every day). Following digitalization the ventricular rate was 84 and the dyspnea, râles and edema were relieved. An electrocardiogram on May 11 revealed persistent flutter, with 3:1 conduction. On September 6, after digitalis had been stopped for two weeks, intravenous Digoxin was administered without alteration of the flutter. Subsequently the patient was redigitalized orally, with attainment of a ventricular rate of 66. He was last seen in the clinic on November 28, 1953, at which time he was well compensated. He died suddenly before his scheduled revisit. No autopsy was performed.

Comment: This case illustrates what is probably the fundamental problem in the treatment of chronic auricular flutter. Digitalis was successful in maintaining the patient's cardiac status, even though it failed to eliminate the chronic flutter. But he died suddenly, and we must consider a cerebrovascular accident as a likely cause of his exitus. It is true that with hypertension he was eligible for both myocardial infarction and cerebral thrombosis. Nevertheless, the possibility of cerebral embolism cannot be excluded. More data are obviously needed for a valid conclusion to be drawn about the danger of thrombo-embolism in chronic auricular flutter. This case points up the importance of obtaining such data.

Case 4. C. H., a 60 year old male, was admitted to Beth-El Hospital on October 2, 1953, because of shortness of breath of two weeks' duration. He was known to have had scleroderma for three years, manifested chiefly by symptoms of Raynaud's syndrome and dysphagia, in addition to signs of involvement of the skin of the face, chest and hands. He had received cortisone over most of this period, with considerable symptomatic relief. He was admitted to another hospital one year prior to admission because of his scleroderma and cardiac complaints (chest pain and dyspnea). An electrocardiogram at that time revealed auricular flutter with 3:1 block. He was discharged improved after a few weeks with no change in the arrhythmia. Two

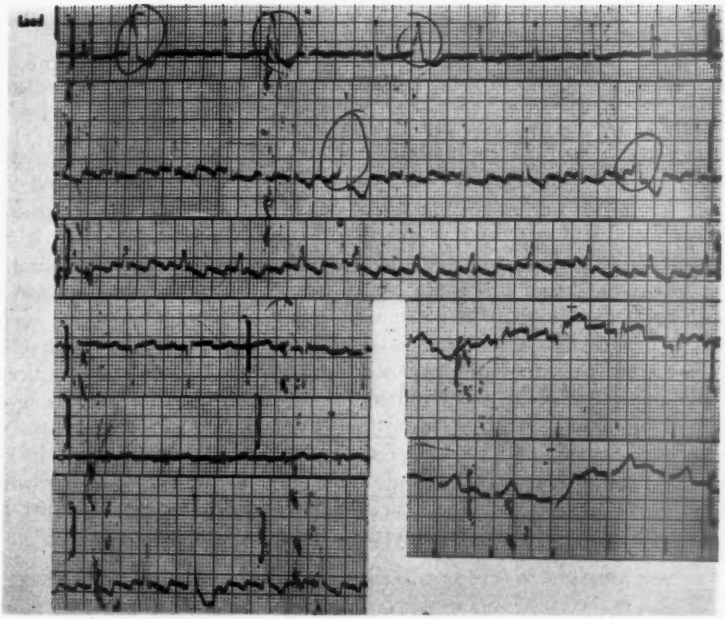

FIG. 3. C. H. Sawtooth flutter waves prominent in Leads II, III, VF. Auricular rate 300, ventricular rate 100 (easily counted in V_1). Patient was discharged from another hospital with diagnosis of auricular fibrillation. Electrocardiograms showed auricular flutter with varying block, and several were so interpreted. Leads I, II, III, aV_R, aV_L, aV_F, V_1, V_2 are recorded in sequence.

weeks prior to admission he again developed exertional dyspnea and orthopnea. A private physician began digitalization one day prior to admission.

On examination the patient was an orthopneic elderly male with scattered sclerodermatous changes of the face, chest and hands. Blood pressure was 130/85 mm. of Hg; ventricular rate was 100 and irregular. The PA diameter of the chest was increased; the breath sounds were decreased throughout. The heart sounds were also diminished in intensity. The liver was palpable four fingerbreaths below the costal margin but there was no edema. The hands showed pigmentation, cold skin, flexion contractures of the fingers and ulcerations of the finger tips.

Course: On admission the patient was placed on Digoxin and a salt-free diet with Mercuhydrin supplements. An electrocardiogram showed auricular flutter. Esophagram showed sclerodermatous involvement of the esophagus. Chest x-ray revealed an enlarged heart, particularly the left ventricle. An electrocardiogram on October 3 showed auricular flutter with ventricular premature contractions (figure 3). An electrocardiogram on October 6 showed auricular flutter with varying AV block. Digitalis was discontinued because of persistent premature ventricular contractions. When these disappeared, maintenance digitalis was re-instituted, controlling the ventricular rate at 60. On October 22 it was decided to employ quinidine to convert the rhythm to regular sinus. A test dose (0.2 gm.) was given at 10 a.m., and 0.3 gm. every one to one and one-half hours for four doses. At 7:30 quinidine was discontinued because the patient complained of vertigo. An electrocardiogram revealed

regular sinus rhythm with bigeminy. At 9:30 p.m. the patient went into collapse, vomited and died.

Postmortem examination of the heart revealed extensive coronary sclerosis, but no recent thrombosis or myocardial infarction. There were no intracardiac or other signs of thrombo-embolism. (The brain was not examined.)

Comment: Postmortem findings in this patient are of some interest because the case pursued a course, often described in the literature and constantly quoted on the wards, of sudden death following restoration of sinus rhythm by quinidine. Few such cases have been autopsied, and it has usually been argued that death in such instances is caused by embolization from auricular thrombi released on conversion of arrhythmia to regular sinus rhythm. This patient had no auricular thrombus. A recent report by Berman et al.[14] is in keeping with our experience. Sudden collapse occurred in four patients with auricular fibrillation and in one with auricular flutter upon treatment with quinidine. In two sinus rhythm was achieved, followed by sudden death. Autopsy revealed no embolization. Two patients were revived by artificial respiration. The authors conclude that many of the reactions following quinidine therapy of auricular fibrillation formerly interpreted as due to cerebral embolization were in reality not embolic episodes at all. They interpret these cases as constituting a "quin-

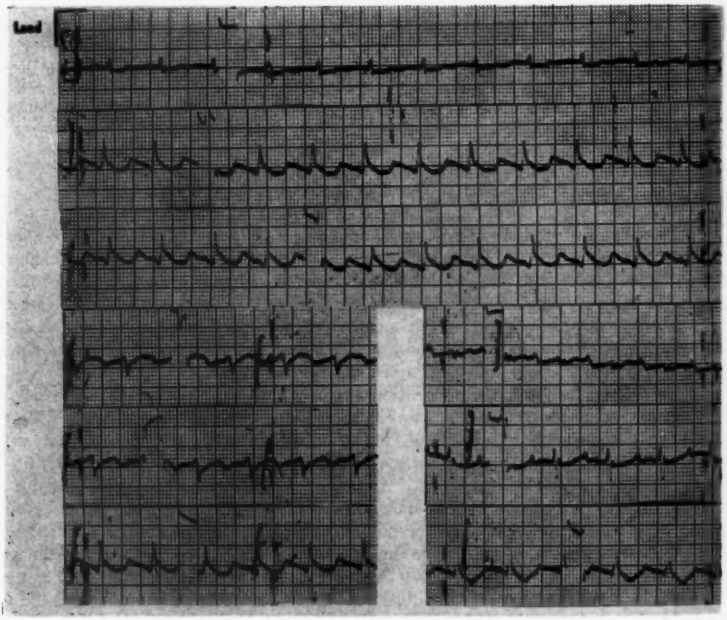

FIG. 4. R. G., 12/29/53. Auricular flutter, auricular rate 210, ventricular rate 105. Leads I, II, III, aV_R, aV_L, aV_F, V_1, V_2, V_5.

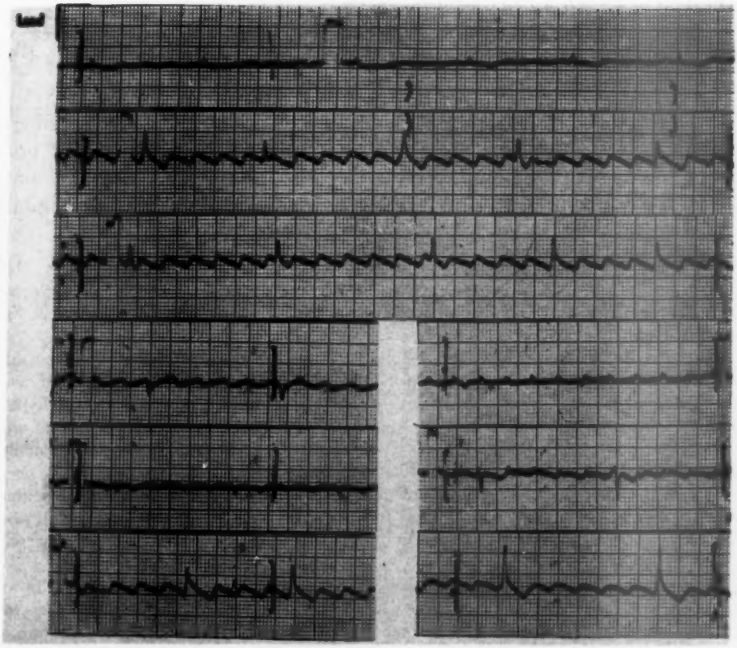

FIG. 5. R. G., 1/4/54. After digitalization. Auricular rate 230, ventricular rate 50.

idine intoxication syndrome." At any rate, the evidence indicates that fatal embolization precipitated by quinidine must be rare, perhaps even nonexistent.

Case 5. R. G., a 35 year old housewife, was admitted to the Beth-El Hospital on December 12, 1953, because of hemoptysis, fever and palpitations. She had developed palpitations two weeks prior to admission. The next day auricular flutter was diagnosed on electrocardiogram and digitalis was prescribed. Two days later quinidine was started and was administered until two days prior to admission. Three days before admission the patient developed fever and hemoptysis. She was known to have had a murmur since childhood.

Physical examination revealed a well developed, well nourished but acutely ill female. Blood pressure, 110/70 mm. of Hg; temperature, 100° F. The ventricular rate was 90 and irregular. Systolic and diastolic murmurs were present at the apex. P_2 was louder than A_2. There were no signs of congestive heart failure, no splenomegaly, no clubbed fingers and no petechiae. There were 7,000 white blood cells, with 80% polys. Chest x-ray revealed an enlarged heart with prominent pulmonary artery segment, interpreted as indicating combined valvular disease. An electrocardiogram revealed auricular flutter (figure 4).

On December 23 quinidine was given, 0.4 gm. every hour, but was discontinued when tinnitus developed. In the ensuing week the patient developed several complications: 1. A temperature of 104° F. without discernible focus of infection, which subsided in a few days. 2. Pruritus of the hands, relieved by Pyribenzamine. 3. Renal colic and hematuria which a genitourinary study showed to be due to a stone, which

was then passed. After two weeks' hospitalization the patient became asymptomatic. The electrocardiogram continued to show auricular flutter with an auricular rate of 214, but the ventricular rate was reduced to 60 by digitalis (figure 5), and the patient was discharged.

Comment: The history suggests that this chronic rheumatic with hitherto asymptomatic mitral stenosis developed auricular flutter two weeks prior to admission. Quinidine and digitalis failed to restore regular sinus rhythm, the flutter persisted, and the patient is being maintained on digitalis to insure a satisfactory ventricular rate.

Case 6. B. W., an 80 year old female, had been under treatment with Mercuhydrin and digitalis for over five years for chronic congestive failure. An electrocardiogram several years before had shown a supraventricular arrhythmia of undetermined nature.

Physical examination revealed a small, chronically ill, somewhat dyspneic and orthopneic female. Blood pressure was 180/100 mm. of Hg. Ventricular rate varied between 120 and 150. Neck veins were distended. The chest was kyphoscoliotic. Heart sounds were of poor quality. The rhythm appeared regular, with runs of irregular beats. The lungs showed bilateral basal râles. The abdomen was soft. Pretibial and ankle edema was present at times.

An electrocardiogram (figure 7) revealed auricular flutter with varying degrees of AV block. (This may be compared with tracing of figure 6 taken several years previously, showing auricular flutter, which was noted only after comparison with the tracing of figure 7.)

The patient was maintained for years on digitalis and mercurials, so that she was able to care for herself and to take short walks. However, her ventricular rate remained very rapid, congestive failure became progressive, and she died despite all therapy.

Comment: Digitalis was never able to control the ventricular rate satisfactorily in this case as it does in the majority of cases. One can only speculate about the part played by kyphoscoliosis. We are also unable to estimate the total duration of auricular flutter in this case. It appears likely that it may have been present for many years, in the same way that auricular fibrillation may persist for many years in chronic arteriosclerotic and rheumatic heart disease.

Case 7. D. B., a 65 year old male, was seen in consultation because of the sudden development of chest pain with a sudden drop in blood pressure.

On physical examination the blood pressure was 140/80 mm. of Hg. The heart sounds were of poor quality but regular. The apical rate was 75. The lungs were clear. The clinical impression was acute myocardial infarction.

An electrocardiogram showed auricular flutter, with an auricular rate of 300 and a ventricular rate of 75. Serial tracings over the next four days revealed persistence of auricular flutter with no signs of infarction.

Course: Later examinations showed no evidence of infarction. Repeat electrocardiogram showed no change.

Comment: Transient auricular flutter is known to occur following myocardial infarction. Conversely, patients are occasionally seen who develop acute coronary insufficiency secondary to paroxysmal tachycardia. In this case serial electrocardiograms showed no evidence of infarction. The ven-

tricular rate was not that of a rapid paroxysmal arrhythmia; moreover, the arrhythmia persisted throughout the period of observation. We cannot estimate the duration of flutter in this case. Unfortunately, the patient is not available for long-term follow up.

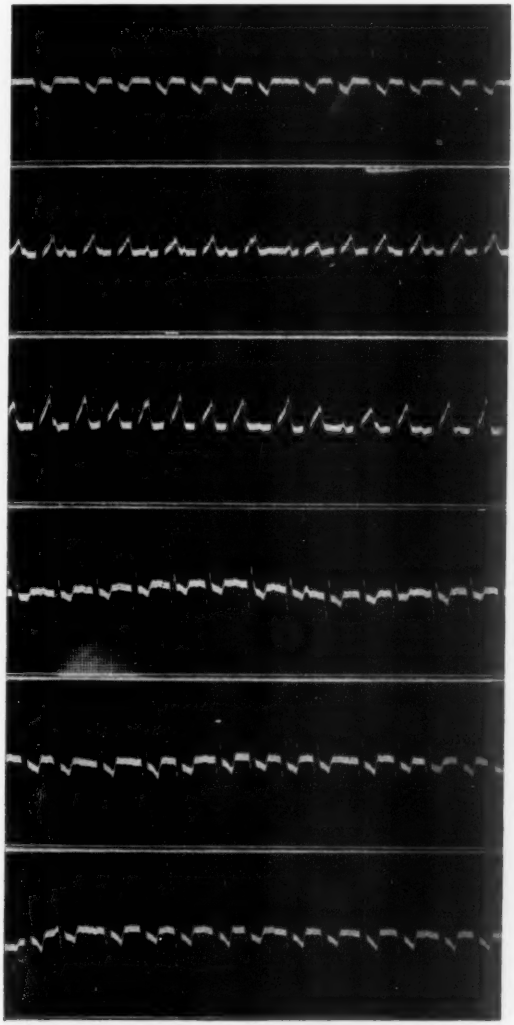

FIG. 6. B. W. Interpreted initially as supraventricular tachycardia with AV dissociation. After subsequent electrocardiogram revealed auricular flutter (figure 7), Lead II was interpreted as probable auricular flutter with varying ventricular response, as in figure 7. Leads I, II, III, CF_A, CF_B, CF_C are recorded in sequence.

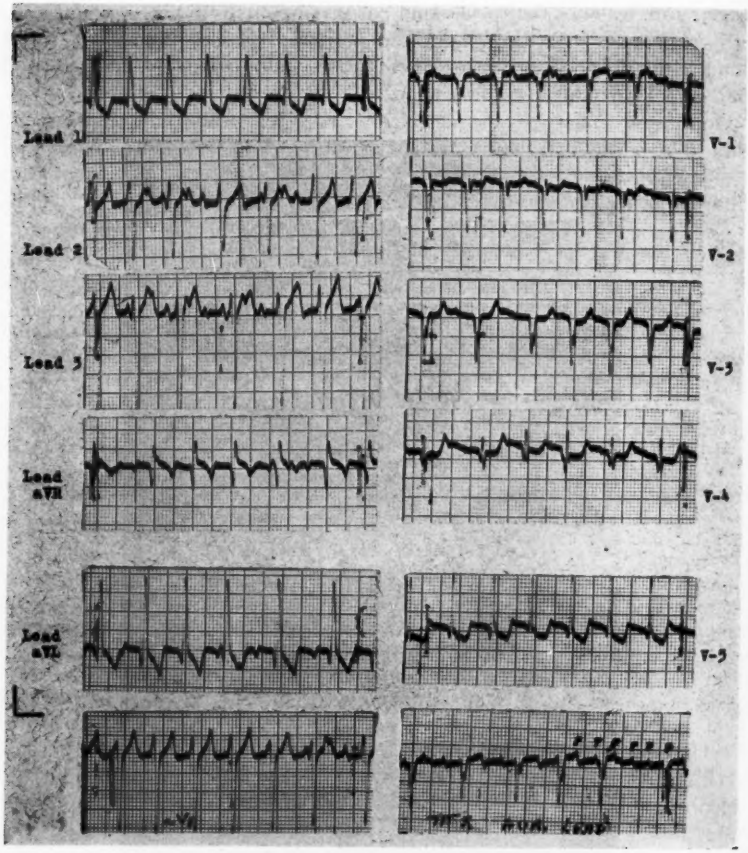

FIG. 7. B. W. Auricular flutter. Auricular rate of 300 may best be counted in auricular Lead IIIR. Ventricular rate varies from 100 to 150 as block varies from 3:1 to 2:1.

In addition to these seven cases with "pure" chronic auricular flutter, we wish to present the record of a patient who forms a bridge between auricular flutter and auricular fibrillation. In electrocardiograms recorded from the right precordium, sawtooth auricular waves are seen at a rate of about 350 per minute, simulating classic flutter except that these waves are not perfectly regular. Such tracings have usually been designated "impure" flutter, or flutter-fibrillation. In McMillan's [15] classic article on auricular flutter there is a series of tracings described as impure flutter which are of the same nature as those in this case. This case is of particular interest because the arrhythmia occurred in association with complete heart block. In the literature of auricular flutter with complete heart block several of the case

reports include illustrations [15, 16b, 16c] which are virtually indistinguishable from those seen in our patient.

Case 8. I. C., a 45 year old male, was known to have had an auricular arrhythmia for seven years (since he first came under observation in 1945).

In October, 1944, after he was injured in an automobile accident, he was told by his physician that he had a heart murmur. The year previously he had passed a physical examination for a double indemnity insurance policy. Following the accident, in November, 1944, he was refused additional insurance because of a murmur.

In March, 1945, the patient was seen by his physician because of palpitations, coryza, cough and xiphoid pain. He later became dyspneic and was referred to one of the authors for consultation. He was found to be in congestive failure, which responded to treatment with digitoxin and Mercuhydrin. After a week in bed he developed severe sharp left flank pain, which was interpreted as splenic infarction. Following this he gradually recovered and returned to work. In September he developed severe pleuritic pain posterior to the axilla. On returning to work he spat blood and developed a temperature of 101° F., and the pain became worse. He was treated with rest and chemotherapy, and gradually recovered. In 1946 digitalis was discontinued and has not been used since. The patient has remained asymptomatic to the present.

Review of systems was negative. There was no family history of rheumatic fever.

Physical examination revealed a well developed, well nourished adult, not ill, and able to lie flat without respiratory distress. Blood pressure was 158/90 mm. of Hg. Fundi were negative. There was no cervical venous distention. There was scoliosis to the left. The cardiac point of maximal impulse was not made out. Left border percussed 12.5 cm. from the midsternal line. The right border was not percussed. The sounds were of fair quality; there was a regular sinus rhythm; the ventricular rate was 52. There was a systolic murmur at the apex. P_2 was greater than A_2. The lungs were clear. There was no hepatomegaly or edema.

Impression: Rheumatic heart disease; mitral valvular disease; auricular flutter; enlarged heart.

X-ray showed the heart to be enlarged to the left; the aorta was of normal size.

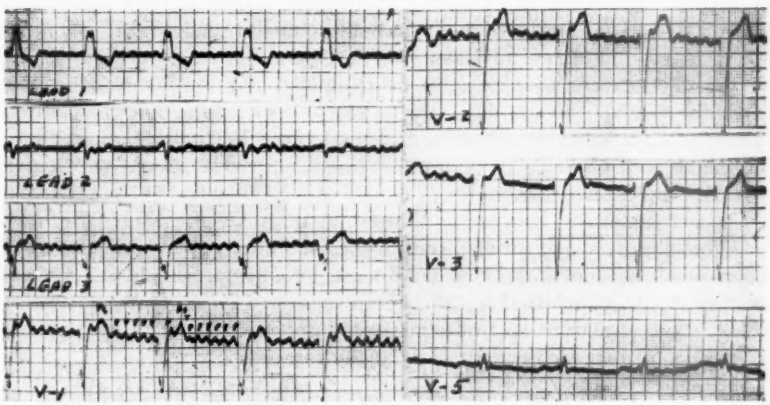

FIG. 8. I. C. Impure flutter with complete heart block. Compare with reference 16b, figures 1 and 5 and reference 16c, pages 143 and 145, reported as cases of auricular flutter with complete heart block.

Many electrocardiographic tracings have been recorded on this patient, all with the same basic disorder (figure 8), impure flutter with complete heart block.

Summary: This patient evidently had chronic auricular flutter, due to rheumatic heart disease with mitral valvular disease. Soon after the onset of cardiovascular symptoms he had several embolic episodes and developed cardiac decompensation. Following the recovery from these complications he has become asymptomatic, although flutter has persisted. He is now leading a normal life without medication.

Comment: If Dicumarol had been popular in 1945 as it is today, one would probably have placed the patient on Dicumarol and then perhaps have attempted to restore sinus rhythm with quinidine. If sinus rhythm had been achieved, his present condition could have been interpreted as the excellent outcome of the therapeutic regimen employed. Since in reality our patient had no such therapy, his remarkable course raises the question of ideal management. One cannot generalize from one case, but neither can one disregard the case.

Summary and Conclusions

The literature of chronic (persistent) auricular flutter is reviewed, and cases of chronic persistent auricular flutter are presented. Emphasis is placed upon the paucity of cases reported in the literature and the scarcity of information on the subject. In all, there are a few case reports and only one large series of cases of flutter in which there is a breakdown into acute (transient) and chronic flutter.

One of the reasons for the rarity of cases of chronic auricular flutter is that the diagnosis is often missed. When there is a varying degree of heart block, auricular fibrillation may be diagnosed clinically and even on the electrocardiogram. When the ventricular rate is slow and regular the clinical impression may be that of regular sinus rhythm. By means of the electrocardiogram, particularly with the so-called auricular lead, cases of chronic flutter are uncovered which have masqueraded under other diagnoses.

It is of importance to know whether persistence of auricular flutter favors development of congestive heart failure and thromboembolic complications. Not enough data are available for satisfactory conclusions. Three patients in our small series died suddenly. Postmortem examination in one showed no evidence of thromboembolism. One patient with coarse auricular flutter has been gainfully employed for the past eight years despite an earlier history of congestive failure and thrombo-embolism.

The ideal management of chronic auricular flutter remains undetermined. In patients without organic heart disease an attempt should be made to restore regular sinus rhythm, as has been suggested for auricular fibrillation. This is a desirable if usually unattainable goal. In most cases it will be necessary to treat each patient individually rather than by a simple formula.

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TUBERCULOUS MENINGITIS: THE DIAGNOSTIC AND PROGNOSTIC SIGNIFICANCE OF SPINAL FLUID SUGAR AND CHLORIDE*

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It is generally agreed that the typical spinal fluid in tuberculous meningitis reflects an elevated pressure, a moderate pleocytosis, an increased protein content and a decline in the sugar and chloride values. The first three of these abnormalities are nonspecific, as, in varying degrees, they will occur with equal facility in a multitude of central nervous system diseases. Hence the greater reliance placed on the concurrent depression of the spinal fluid sugar and/or chloride. It has been the policy of the Los Angeles County General Hospital Tuberculosis Service to measure both the spinal fluid sugar and chloride in every case of tuberculous meningitis, both as an aid to diagnosis and as a means of following the course of the disease. Others [1, 3, 4, 5] stress the changes in the spinal fluid sugar and have more or less discontinued chloride determinations as a routine. It is the objective of this study to assay the diagnostic and prognostic significance of these determinations, and to ascertain the necessity or desirability of examining both these factors when the clinician is called upon to diagnose and treat meningeal tuberculosis.

Material and Methods

This study includes 231 cases (205 treated and 26 untreated) of meningeal tuberculosis of all age groups observed at the Los Angeles County General Hospital from 1947 through 1953. Our therapeutic methods are not germane to this study, but do not differ materially from those employed at other tuberculosis centers.

To evaluate the diagnostic significance of sugar and chloride levels we have studied the initial spinal fluid in each case in which a complete chemical analysis was done. Each of these cases was placed in one of four categories, viz.: (a) normal sugar-normal chloride, (b) depressed sugar-normal chloride, (c) normal sugar-depressed chloride, and (d) depressed sugar-depressed chloride. Normal values in our laboratory have been established at 50 to 80 mg. per 100 c.c. for sugar, and at 120 to 130 mEq./L. for chloride. The series of spinal fluids obtained on each case during the first few days of hospitalization, i.e., the diagnostic period, was similarly classified into one of these four categories.

* Received for publication May 5, 1954.
From the Tuberculosis Service of the Los Angeles County Hospital.

To evaluate the prognostic importance of these spinal fluid components, we have attempted (a) to correlate the survival rates of treated cases for each of the abovementioned four categories, (b) to correlate the magnitude of the fall of the sugar and of the chloride with survival, and (c) to evaluate the relative merits of sugar versus chloride decline as an indicator of relapse.

Results

The diagnostic significance of the depressed sugar or chloride is illustrated in table 1. When only the *initial* (admission) spinal fluid examination is considered (table 1, A), it will be noted that of the 161 patients in whom both sugar and chloride were examined, 109 (68%) revealed a decline in both these factors, 12 cases (7.5%) displayed normal figures for both tests, 12 cases (7.5%) presented a unilateral sugar depression, and 28

Table 1

	(A) Initial Examination		(B) Diagnostic Period	
	No. of Cases	% of Total	No. of Cases	% of Total
Normal sugar Normal chloride	12	7.5	4	1.7
Depressed sugar Normal chloride	13	7.5	13	5.6
Normal sugar Depressed chloride	28	17.0	46	20.0
Depressed sugar Depressed chloride	109	68.0	168	72.7
Total	161*	100.0	231	100.0

* Only 161 of the 231 cases had quantitative sugar and chloride determinations on the initial spinal fluid.

cases (17%) revealed a unilateral fall in chloride. Thus there were 40 (25%) normal sugar and 24 (15%) normal chloride values in the 161 initial spinal fluid examinations.

In the *diagnostic period* (first few days of hospitalization) it will be seen from table 1, B that of the 231 patients only 4 cases persisted with normal sugar and chloride levels, 13 (5.6%) realized a decline in sugar without concomitant effect on chloride, and 46 (20%) displayed a unilateral chloride depression, while 168 cases (72.7%) evolved the customary decline in both factors. It would appear that few patients with normal sugar and chloride values on initial examination maintain this normalcy during the entire diagnostic period. But whereas 50 patients (32%) maintained a normal sugar value, only 17 (7.3%) maintained chloride levels which failed to reflect the meningeal infection during the diagnostic period.

The prognostic implications of the various spinal fluid chemistry combinations are shown in tables 2, A and 2, B. In general, little prognostic cor-

TABLE 2 (A)

Survival as Reflected by the Initial Spinal Fluid Sugar and Chloride Values
(Treated Cases Only)

	No. of Cases	Alive	Dead	% Survival
Normal sugar Normal chloride	11	9	2	81.8
Depressed sugar Normal chloride	12	6	6	50.0
Normal sugar Depressed chloride	26	10	16	38.4
Depressed sugar Depressed chloride	92	30	62	32.6
Total	141	55	86	39.0

relation is apparent. When the sugar and chloride values remain normal, the survival rate is apparently better than when either or both are depressed. When either the spinal fluid sugar or the chloride was depressed, the prognosis dipped to approximately 50% survival, without a distinction of significant statistical merit warranted as to whether it was the sugar or the chloride factor that reflected the disease process. When the customary combination of depressed sugar-depressed chloride presented, survival fell to approximately 35%.

When we sought to determine the predictability of survival by means of correlating recovery rates with the depth to which the spinal fluid sugar plunged (table 3, A), little enlightenment was forthcoming, since the survival rates in patients whose spinal fluid sugar at no time dipped below the normal range were only slightly better than those with sugar values between 30 and 50 mg.% (approximately 54% and 44%, respectively). However,

TABLE 2 (B)

Survival as Reflected by Spinal Fluid Sugar and Chloride Values
during the Diagnostic Period
(Treated Cases Only)

	No. of Cases	Alive	Dead	% Survival
Normal sugar Normal chloride	4	4	0	100.0
Depressed sugar Normal chloride	13	7	6	53.8
Normal sugar Depressed chloride	42	19	23	45.0
Depressed sugar Depressed chloride	146	51	95	35.6
Total	205	81	124	39.5

when the spinal fluid sugar depletion fell below 30 mg.%, only 32.3% of the patients recovered. Hence one is left with the rather obvious deduction that persistently normal spinal fluid sugars suggest a better prognosis than those which are markedly depressed.

A somewhat better correlation with survival for graduated levels of spinal fluid chloride depression seems definable in table 3, B. Here, too, no

TABLE 3 (A)
Correlation of Lowest Spinal Fluid Sugar Value with Survival
(Treated Cases)

Mg. %	No. of Cases	Alive	Dead	% Survival
Above 50	22	12	10	54.5
45–49	1	1	0	44.4
40–44	17 } 18	7 } 8	10 } 10	
35–39	25	12	13	43.5
30–34	44 } 69	18 } 30	26 } 39	
Below 30	96	31	65	32.3
Total	205	81	124	39.5

prognostic distinction could be realized with mild depression. Only where the fall in chloride was beyond 110 mEq./L. was any correlation apparent. However, when low values for chloride plummeted below 100 mEq./L., only 27% survived. Although neither is well pronounced, it seems that of the two the chloride level serves as a slightly better prognostic yardstick.

In this series of patients there were 100 whose clinical improvement was

TABLE 3 (B)
Correlation of Lowest Spinal Fluid Chloride Value with Survival
(Treated Cases)

mEq./L.	No. of Cases	Alive	Dead	% Survival
Above 120	8	6	2	75.0
115–119	5	4	1	73.9
110–114	18 } 23	13 } 17	5 } 6	
105–109	45	17	28	40.5
100–104	39 } 84	17 } 34	22 } 50	
Below 100	90	24	66	26.6
Total	205	81	124	39.5

interrupted by a temporary or permanent recrudescence. We attempted to compare the propensity of serial spinal fluid sugar versus chloride determinations in heralding these clinical relapses (table 4). It was found that 10 cases were first reflected by a unilateral drop in sugar content, whereas chloride depression by itself served as the harbinger of relapse in 46 of the cases. A simultaneous decline in sugar and chloride values was found in 32 instances. Death intervened unheralded in 12 of the 100 cases, and even

TABLE 4

Spinal Fluid Sugar and Chloride in Relapse

	No. of Cases
Declining sugar as first spinal fluid evidence of relapse	10
Declining chloride as first spinal fluid evidence of relapse	46
Simultaneous decline of sugar and chloride as first spinal fluid evidence of relapse	32
No change in spinal fluid sugar or chloride in face of relapse	12
Total	100

in retrospect could not have been presaged from analysis of the spinal fluid chemistry determinations.

DISCUSSION

As a result of clinical impressions gleaned from day-to-day personal supervision of tuberculous meningitis patients at the Los Angeles County General Hospital in the past seven years, we have come to place considerable reliance on the value of the spinal fluid chloride determination. Our study was undertaken to evaluate this clinical impression objectively. Material was extracted from 231 cases of meningeal tuberculosis seen at the Los Angeles County General Hospital between the years 1947 and 1953. The over-all survival rate was 39.5%. With regard to the diagnostic significance of the sugar and chloride components of the spinal fluid, our findings show neither to be infallible, but of the two, the chloride diminution occurred with significantly greater frequency than did that of the sugar. This diagnostic superiority of chloride over sugar was maintained even after we excluded from consideration those cases whose normal spinal fluid sugar values might have been incidentally produced as a result of their having received intravenous glucose feedings shortly before the time of spinal fluid withdrawal. In general, our findings with regard to the prognostic significance of the spinal fluid sugar and chloride would indicate that neither is a particularly accurate or sensitive forecaster. But again, of the two we find the chloride to be somewhat more of a prognostic indicator than the sugar.

These findings are not in complete accord with those of some observers.[1, 4, 5, 6, 8] This series deals with patients of all ages, which may make it not comparable to studies limited to either children or adults. Then, too, a majority of our patients are in advanced stages of their disease when first seen by us. Many are in coma or semicoma, and in some instances they have been receiving intravenous infusions of glucose. Bunn,[2] in his study of 43 cases of meningeal tuberculosis treated in Veterans Administration hospitals, avers that no one spinal fluid test can be relied upon exclusively in either the diagnosis or the prognostication of survival in this malady. His statistics for immutable sugar values during the diagnostic period are not greatly divergent from ours. Spinal fluid chloride determinations as an aid to diagnosis are not prominently mentioned in his study,

although on another occasion [3] it was disclosed that as many as one third of the meningitis cases had persistently normal chloride levels. This last figure is in variance with our finding of only 7% maintaining an unfalling chloride content during the diagnostic period. One possible explanation for this discrepancy may lie in the more advanced state of the illness which we customarily encounter. In variance with this V.A. study, too, was our finding of a favorable prognosis with the persistence of normal sugar and chloride values through the diagnostic period. There is agreement, though, in that no significant prognostication of survival could be hazarded when either the sugar or the chloride was depressed. We were in agreement, too, in that we found no consistent prognostic significance in the depth to which the sugar or the chloride fell during the illness, except when the decline was of an extreme nature.

When we compared spinal fluid sugar with spinal fluid chloride as a relapse indicator, we found that serial determinations of both components will stand the clinician in good stead, since at times one, and at times the other, heralded clinical recrudescence. Of the two factors, though, the chloride appeared the superior, since, alone or in combination with sugar, it served as harbinger of relapse in four fifths of the cases, whereas sugar declivity under the same circumstances played a rôle in only two fifths.

In general, we found the spinal fluid sugar less reliable than the chloride examination in meeting our clinical needs. Several explanations suggest themselves for this seeming vulnerability of the spinal fluid sugar determination. Of importance is the alacrity with which the spinal fluid sugar reflects the blood sugar level so long as diffusion across the blood-spinal fluid barrier is unimpaired. Thus, in the hyperglycemic state, i.e., diabetes or intravenous glucose administration, the spinal fluid sugar is unreliably elevated. Indeed, we have discovered more than one case of diabetes mellitus as a result of a very normal spinal fluid sugar in the presence of meningeal tuberculosis with an otherwise characteristic fluid. Similarly, when we went back to the clinical records of the patients in this series with persistently normal spinal fluid sugars, we found that several had been receiving glucose by vein throughout the diagnostic period. Conversely, an initially low spinal fluid sugar may be reflecting hypoglycemic starvation secondary to protracted vomiting or inadequate nutritional intake. Friedman et al.[7] discuss the inhibitory effect of intramuscular or intrathecal streptomycin on meningeal cellular carbohydrate metabolism in tuberculous meningitis, and use this postulate to explain the failure of some cases to manifest the expected fall in spinal fluid sugar when meningitis supervenes in the face of streptomycin treatment. Also, when the diffusion across the blood-spinal fluid barrier is impaired, spinal fluid sugar determinations might be unreliably low if replenishment from the blood is delayed and inadequate, or unreliably high if the diffusion factor is not appreciably altered but the fibrotic meninges are no longer so glycolytic. Then, too, the glucose content of spinal fluid specimens may decline if laboratory examination is delayed.

Hence, we feel that the spinal fluid sugar determination is not in any sense infallible, and that in this complex disease no one determination should be emphasized to the exclusion of others. Because the routine examination of the spinal fluid chloride has been so valuable in our experience, we suggest that it be included in the diagnostic armamentarium when tuberculous meningitis is suspected.

Summary

A series of 231 cases of tuberculous meningitis observed at the Los Angeles County General Hospital has been analyzed to ascertain the diagnostic and prognostic significance of the spinal fluid sugar and chloride levels. Both factors were depressed in most instances, but in a significant number of cases one or the other was normal at the time of the initial examination and remained so throughout the diagnostic period. In our series the sugar levels failed to reflect the meningeal tuberculosis more often than did that of the chloride. Neither the spinal fluid glucose nor chloride provides a sensitive prognostic index. But again, of the two we find the chloride to be somewhat more reliable. It is therefore recommended that chloride determinations be part of the routine spinal fluid analysis in tuberculous meningitis.

Acknowledgment

Appreciation is herewith expressed to the Los Angeles County Tuberculosis and Health Association for its aid in this study.

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THE TREATMENT OF EMOTIONALLY INDUCED ILLNESS IN GENERAL MEDICAL PRACTICE BY AN AUDIOVISUAL TECHNIC *

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INTRODUCTION

The Number One Problem in Contemporary Medicine: The contemporary physician is aware of two painful facts.

The first is that emotionally induced illness comprises the bulk of medical practice. If the diagnosis of emotionally induced illness is confined to nonstructural illness, the incidence is around 30% of all patients seen.[1] If the diagnosis is allowed to include structural change, the incidence is upward of 70%. Emotionally induced illness is thus by far the most important present day consideration in public health.

The second fact is that the physician's treatment for this illness is easily the poorest he has to offer for any disease. Added to this therapeutic impotence is the frustrating consumption of office time, and the even more frustrating repeat engagements at which the patient remarks, "Doctor, I'm no better; if anything, worse." The therapy usually given is generally of little permanent value for the patient, but is even worse for the doctor.[1] No other group of patients sap the spirit of the doctor so much, or make the doctor feel so ineffectual—to the point of never wanting to see another patient again; no other group aggravates, irritates or frustrates him so much as these. These are the difficult patients who, with their relatives, do the greatest damage to our crust of composure, equanimity and decorum, who often drive us to distraction.

Because this illness needs and deserves a more adequate method of therapy, an internist like myself with but a minimal amount of psychiatric training may possibly be forgiven for suggesting a new form of treatment, especially since it is a form far removed from contemporary psychiatric methods. Desperation produces many oddities, perhaps none greater than the method described in this paper.

The Impossibility of Traditional "Adequate Psychotherapy": The method termed "adequate psychotherapy" is out of the question for the majority of patients with emotionally induced illness. Omitting all consideration of its effectiveness in the individual patient, its use on more than 1% of patients is impossible simply on the basis of time. "Adequate psychotherapy" requires 10, 15 and more nearly 20 hours per patient. By working 20 hours a day, the physician could see the equivalent of one patient per day. The average physician must see 23 patients a day, 14 of whom have emotionally induced illness.

* Received for publication June 7, 1954.

The Therapeutic Answer Must Lie in Some Unexplored Direction: The problem is obvious, the answer is not, but the answer must lie along some line not utilized by psychiatry in the past. At least that is part of the apology for the present paper.

The method of therapy presented in this paper may best be termed "an audiovisual presentation of the learning-maturity concept." It has been gradually evolved from a beginning with group therapy over a period of 20 years, and in its more or less final form has been given to thousands of patients.

Quite aside from its therapeutic effectiveness, it is of interest because it requires no more of the physician's time than is necessary for a good physical examination.

The Salient Principles of the Method

The Learning-Maturity Concept and the Audiovisual Technic: By the method described in this paper the physician can give hours and hours of directive therapy to the patient by means of an automatic linking of tape recordings and projected Kodachrome slides.

Obviously, traditional psychotherapy does not lend itself to this technic. The basic concept in the present method of treatment is the *learning-maturity concept,* which has been gradually emerging from the boiling cauldron of psychiatric and psychologic thinking.[2, 3, 4] By its very nature, the *learning-maturity concept* lends itself admirably to audiovisual presentation of the kind described herein.

The basic idea in this concept is that stress arises in people because they are trying to handle adult situations and problems with primitive and childish technics. In other words, emotional stress is the result of mis-education, or lack of proper education, and emotional stasis can be achieved by *learning* the qualities which comprise *maturity.*

The learning-maturity concept is to a considerable extent the antithesis of Freudian psychiatry. The latter is based on the concept that emotional stress is conditioned early in life by an unacceptable experience which is repressed into the murkiness of the subconscious, where it preys on the host forevermore. For the psychoanalyst, and indeed for most of the traditional psychiatrists today, therapy consists largely in an attempt to find and bring into conscious focus the repressed elements.

The learning-maturity method has an interest in the past to the extent of the physician's wishing to know the patient's type of immaturity, but this can be determined with sufficient accuracy without hours and hours of couch talk. Furthermore, regardless of the omissions and commissions of his past, the patient *must start in the present* to acquire a working degree of maturity so that the future may be better than the past. The present and the future depend on *learning* new habits and new ways of looking at old problems. Rather than emphasizing a magnified portion of the past, as does the conditioning concept, the learning-maturity concept emphasizes the need for

learning an improved approach to meet the adult problems of today and tomorrow. The delightful aspect of this simple and seemingly naive approach is that it works.

The Common Denominator in Emotionally Induced Illness: Every patient with emotionally induced illness can receive the same treatment because the underlying emotional problem can be reduced to the same common denominator in every patient.[5] This common denominator is the fact that the patient has forgotten—or perhaps never learned—how to control his thinking to produce *enjoyment* of the present moment. Instead, he has developed the habit of reacting to ordinary situations with constant fear, anxiety, apprehension, irritation, frustration and discouragement, all of which absolutely preclude the possibility of enjoyment.

What the patient needs to learn is how to react to situations with equanimity, courage, determination and cheerfulness. This is the same as saying "with maturity."

Maturity is the same thing in one person as in another.

Therapy for a condition caused by immaturity can be standardized to one general and inclusive pattern.

Types of Patients Most Suitable for Audiovisual Technic: An important point becomes apparent in a general medical practice which is not apparent in the type of patient who ultimately comes to the psychiatrist, and that is that there are two fairly distinct groups of patients with emotionally induced illness:

1. The first group, comprising at least 85% of the total, have their monotonous repetition of apprehensive emotions producing physical symptoms as the result of *stressful life situations* with a *lack of know-how in meeting these situations.* The latter is the result of faulty educative processes in their past.

2. The second, and smaller, group, comprising less than 15% of the total, have their monotonous repetition of apprehensive emotions because of a profound conflict in their personality. These personality conflicts are made apparent by the accompanying mental reaction: dissociation, conversion, phobias, obsessions or depression.

The second type, not the first, is the one that comes to the psychiatrist.

I am sure that many of the things psychiatrists say about emotionally induced illness seem to us internists to be questionable because we infer that what the psychiatrist says about group two is also true of group one. As a matter of fact, almost nothing that is true of group two is true of group one except the fact that in each the physical symptoms are physiologic manifestations of the emotions and are not purposeful, are not defensive, and are not "organ language."

The audiovisual technic described in this paper is tailor-made for group one, and is very successful in this class of patients. But the technic is distinctly worth while for patients of group two, and some of our most delight-

ful successes have come from group two. Group two patients are definitely more difficult, and may have to repeat certain portions of the sessions several times. Most of the frank failures with the method occur in group two. If the mental reactive state of patients in group two is in an early stage the method is highly successful. However, an increasing state of confusion and dissociation interferes with the reception of directive therapy, just as it does with traditional psychotherapy. The frankly confused and muddled depressive and melancholiac is given electroshock therapy for five or six days, following which, and while he is still in the hospital, he attends the audio-visual sessions daily. Two to four weeks later, while his memory is returning, he again attends the sessions daily. This procedure greatly lengthens the succeeding well period and decreases the likelihood of a return of the depressive state. The most difficult patient is the one in group two who is at the halfway stage in his confusion—he is beyond the early, readily receptive stage, already too far advanced in his reactive mechanisms to be receptive to directive technic, yet he and his family do not think he requires electroshock therapy. These constitute most of the failures.

The method will be described in general, with emphasis on a few details.

The Initial Psychotherapy of a Thorough Examination

Psychotherapy Begins with the Registration of the Patient: The therapy starts the moment the patient steps into the office. The physician and his aides must impress the patient as being sincerely interested, understanding and sympathetic, and, above all, thoroughly capable.

The Examination Must Be the Best the Patient Has Ever Had: The examination is one of the most important parts of successful therapy, and unless it is done properly it is useless to spend the patient's time and money with any form of directive therapy.

The examination must be the most thorough and complete the patient has ever had, or he will in the end prefer to believe some previously consulted physician who gave him a better examination and an organic diagnosis. Yours must be the examination to end all further examinations.

The Cornell Medical Index: An excellent beginning is to have the patient fill out a Cornell Medical Index while he is in the waiting room. This carefully compiled set of 195 questions tells you many things, but—and probably most important—it tells you at a glance what apprehensions concerning himself the patient has in the back of his mind.

Be Careful to Be Meticulous and Thorough: Your physical examination cannot possibly be too complete. The x-ray and laboratory studies must cover every apprehension and concern which your careful history warned you the patient has. Every idea of organic disease which the patient might later conceivably clutch to his bosom must be precluded by your examination. If the patient has had even a little bleeding from the rectum, it would not only be bad medicine but also a bad block to further psychotherapy not to do a

rectal examination, a sigmoidoscopy and a roentgen colon study. If the patient has a fear about his heart, it is useless in this day and age to tell the patient, "I know your heart is perfectly normal," and proceed without an electrocardiogram. The patient has heard about electrocardiograms and has the same magnified opinion of their importance that many physicians have. One week after you have started your therapeutic efforts, such a patient will stop you cold in your tracks by saying, "But what about my heart, doctor? You didn't x-ray it, and you didn't get an electrocardiogram." You must then give an unimpressive explanation of why you were not thorough or complete, or you must beat a retreat from your functional diagnosis by doing what the patient wants. Either procedure seriously impairs your therapeutic effectiveness. Do *first* every examination which your careful history tells you the patient will be concerned about. If somewhere along the line he has picked up some thyroid information or concern, you had better have a basal metabolic rate to counter the future thyroid sallies he is sure to make. The only economy for the functional patient is to make it unnecessary for him to do any more shopping from doctor to doctor, from treatment to treatment, from surgery to surgery.

Reviewing the Examination with the Patient: The stage of examination is finished when the patient returns to my office from his last special examination.

I review briefly but completely the results of every part of the examination, translating it always into his terms.

Then I end the interview by saying something like this: "Your physical health is good. Every part of your body is in very good condition. But there is obviously one thing wrong with you, and only one. Although every part of your body is in good condition, the parts are not functioning properly. You are like a railroad on which all the equipment is in apple-pie order—the rails, the engines, the cars, everything. But the chief dispatcher is getting everything balled up. The railroad is perfectly good, but it isn't functioning properly. And the same sort of thing is true of your organs: they are not functioning properly. I want you to come in at nine o'clock tomorrow morning with your wife (or husband), and I will show you what functional trouble is, how it works, and how we are going to fix it."

Directive Therapy by Audiovisual Technic

The Physical Arrangement and Materials: The next morning at nine the doctor conducts the patient and his wife to a room with comfortable chairs, and tells them that what they are about to hear is the explanation of functional disease. Here, in private, the patient and spouse listen to tape recordings illustrated by colored lantern slides (Kodachrome). The projection machine is an automatic variety which changes slides at a signal from the tape recording.

These private sessions with tape recordings and slides require an average

of 10 hours and a maximum of 15 hours per patient. The first day the patient receives five hours—from 9:00 a.m. to 3:00 p.m., with periodic stretch periods. Three to six days later he receives two hours, then one or two hours a week. One of the periods at present consists of a colored sound movie. But we have found that this is no more effective than the tape-slide presentation, and it is much more expensive and difficult to produce. In the future the movie will be replaced by tape-slides.

Besides this one hour moving picture, the materials for the total presentation include a tape recorder (wire recorders have been discarded as troublesome), 15 hours of tape recordings, an automatic slide projector and 820 Kodachrome slides.

At the present time the tape recorder is centralized in the doctor's office and is wired to the room occupied by the patient, where he hears it from a loud speaker. Any number of rooms can be wired from the same recorder and patients in different rooms with their own projectors can be treated simultaneously. If one lacks this set-up, it is feasible to have two, three or at most four couples attend the presentations in the same room. There are distinct advantages, however, in the private-room arrangement. The husband and wife then feel free to talk and to call each other's attention to what, to them, are significant points in the program. They also feel that the presentation is distinctly *for them.*

The patient sees the doctor briefly before and after each audiovisual session, mainly to clear up points, to allow the patient to express what he has been repressing, and to help the doctor in successfully orienting the patient.

After each presentation the patient is given readings in a handbook covering the material that has been presented audiovisually. This handbook, written by the present writer, is published by Prentice-Hall, Inc., under the title, *How to* Live *365 Days a Year.* It covers all the material in the audiovisual sessions. The patient thus hears the tape, sees the slide, reads the handbook, and has the doctor's guidance.

The Period of Explanation: Traditional psychotherapists have trouble convincing the patient that his aches, pains and other symptoms are emotionally induced, and the average patient is left semi-convinced. The psychiatric explanations have usually been based on the idea that the symptoms are purposeful (which is bad psychology) or, more commonly, on the idea that symptoms are organ language of the patient's difficulties. For example, a patient was given this explanation of his diarrhea: "You hate and reject your mother-in-law, and you would like nothing better than to have her out of your life. Your diarrhea is your body's language expressing that repressed desire." Another patient was told: "You feel a lump in your throat as an expression of the fact that there are many things in your life you can't swallow." And so on. The average patient remains a bit skeptical of such symbolic explanations. That there was a connection between the mother-in-law and the diarrhea there was no doubt, and between the patient's situa-

tions and the lump in his throat. But the actual mechanism is not one of organ language, which is the psychiatrist's symbolization rather than the body's.

The actual connection is a physiologic one whose mechanism is becoming well understood. Many psychiatrists have recently veered from symbolic explanations toward physiologic explanations,[6] and it is a physiologic explanation that is given the patient in the audiovisual sessions.

The first three hours of audiovisual presentation show the patient the physiologic mechanism of about 40 of the most common symptoms in emotionally induced illness.

As an introduction, the patient is shown how organic disease of one or two organs acts. Then functional disease is described as producing almost exactly the same symptoms. The patient is assured that functional symptoms—the pains, numbnesses, vertigos, etc.—are not imagination, but as real as the symptoms of a broken leg. He is also assured that practically everyone at some time or other has functional disease. It is his turn now; some day it will be the turn of the fellow who at present may be belittling the symptoms the patient has. He is further assured that functional disease is readily curable by the proper means, but that antiquated methods of substitution therapy may result in prolonged chronicity.

The patient's disease is referred to as "functional disease" during this period of explanation. Later, when he understands the role of emotions, it is referred to variously as "stress disease," "emotionally induced illness" or "functional disease." The terms "neurosis" and "psychoneurosis" are never used, since they would place the patient on a nonreceptive defensive, and because the terms contain so many connotations that are not true of emotionally induced illness that they are best used with caution.[7, 8]

After the introduction, the patient is ready to be told that functional disease is due to the wrong kind of emotions. An emotion is clearly and carefully defined on the Lange-James physiologic basis as "a state of mind that manifests itself by sensible changes in the body." The slightly differing mechanism of Dr. Cannon's theory would work as well. Illustrations are given of common emotion-symptom complexes, such as disgust-vomiting, fear-fainting, anger-coronary occlusion. The mechanism of each is explained. Then a series of symptoms mediated by the autonomic nervous system are described, using the materials of Wolf, Wolff, Dunbar, Altschule and others. Next, the endocrine mediation of symptoms is explained, using the work of Dr. Hans Selye and others. This last involves the introduction of organic disease emotionally induced, and these conditions are afterward referred to as "stress disease."

To get the patient to sit through three hours of explanatory material, it must be presented in an absorbingly interesting way. This has been achieved through long practice. Almost without exception (and the exceptions are the confused patients of group two), the patient comes away enthralled. He is enthusiastic in the knowledge that at last someone under-

stands him and has shown him what is wrong. He is apt to say, "Sure, you were describing me all the time. Why didn't someone tell me before how this worked?"

At least 90% of the patients come out of the explanatory period sold on the idea that their own trouble is emotionally induced illness. They are in a receptive mood for directive therapy, which is begun the same afternoon.

The Period of Ventilation: In traditional psychotherapy the period of ventilation and the period of education which follows are quite separate and distinct units. In the audiovisual method the ventilative and educative periods dovetail at all points. But we will consider them separately here to make clear the steps in each.

In traditional psychotherapy the major amount of time is spent in having the patient ventilate about himself and his past. Many psychiatrists consider this ventilation to be the most important part of the therapy. And some would agree that *only* the period of ventilation is of therapeutic value, and that any attempt at education is valueless. The traditional psychiatric ventilative period lasts an hour, and is repeated at weekly intervals for months or years, the length of time being determined by the patient's response or the therapist's inclinations.

In the audiovisual technic, ventilation by the patient is obviously impossible, and with the learning-maturity concept it is unnecessary. Here, instead of the patient's ventilating to the doctor, the doctor ventilates *for* the patient.

In the audiovisual sessions the doctor shows the patient the causes for emotional stress. The presentations begin with simple situational factors, and progress to the more complex personality factors. The material is always presented by actual example. Abstractions are avoided. Separate sessions handle family factors, sexual factors, occupational factors. The patient is awakened to new views of human personality. He is made to become aware of factors in himself which are producing stress. Actually he learns far more about himself, and about human beings in general, in six hours of audiovisual sessions than he could in six months of ventilation.

All stress-producing factors, from situational to personality maladjustments, are interpreted as occurring because the individual is handling adult situations with immature technics, or because the individual is unknowingly suffering from the lack of one or more basic psychologic needs.

With some alterations, the picture of maturity that is given the patient is that of Saul:[4]

1. A feeling of *independence* and responsibility.
2. A *giving* instead of a receiving attitude.
3. A spirit of *coöperativeness and human sympathy* instead of egoism and selfishness.
4. An acceptance of the social restrictions on sex and of making sexuality a successful part of a happy marriage.

5. A feeling for the *human enterprise,* with *kindliness* and good will instead of childish hostilities, anger, hate, cruelty and belligerence.

6. An acceptance of the need for *flexibility* and *adaptability* before unalterable circumstance.

7. An ability to turn defeat into victory instead of into frustration.

8. A liking for work and a desire to do a job well.

9. An ability to make the present moment enjoyable instead of worrying about the past and future.

The basic psychologic needs, the absence of any one of which will give a person a feeling of restless uneasiness and insecurity, are these:

1. Love and affection from others.
2. Security.
3. Avenues of creative expression.
4. Recognition for one's efforts.
5. Opportunity for new experiences.
6. A basis for a measure of self-esteem.

The Period of Education: Teaching the patient how to meet the run of situations in life, and how to compensate for the lack of any of the basic psychologic needs, is the educational aim of the learning-maturity method.

Although every patient is given a similar review of the qualifications and practice of maturity, certain specific aspects are developed for others whose maturity needs educating in certain fields, such as sex, family, living or handling the problems of the aged.

In all these directive sessions the terms of maturity are always translated into practical, concrete ways of handling everyday living.

Thus, at the onset the patient is told to keep *one* idea always in mind, repeating it over and over, so that acting upon it becomes a conditioned reflex.[5] This one idea is, "I am going to keep my attitude and thinking calm and cheerful—right now." As the correlation of this key thought, the patient is to practice thought control and to check himself the moment he finds himself becoming anxious, worried, apprehensive or discouraged. Having checked his rush into a stressing emotional state, he consciously substitutes a train of thought that will produce some degree of equanimity, courage, determination and cheerfulness. This simple ability to produce something enjoyable out of the present moment is the thing which the patient must practice and practice. He is shown specifically what direction his mind can take under various situations and circumstances.

Keeping the discussion on this practical level, the patient is shown how to (1) keep life simple, (2) avoid watching for a knock in his motor, (3) like work for work's sake, (4) develop a good hobby, (5) be satisfied with situations that cannot be changed, (6) like people, (7) say the cheerful, pleasant thing, (8) turn the defeats of adversity into victories, (9) meet problems with decision, (10) emphasize the importance of the present moment, (11) be always planning something, (12) say "nuts" to irritations.

Putting these directives into practice constitutes a good part of maturity and produces emotional stasis. The patient is shown how they may be applied in family living, in sexual life, on the job, in the aging years.

There is enough repetition from varying angles so that the patient finally is given a very definite pattern for action. He usually finds his new tools for living to be much more enjoyable and effective than the ones he discards.

Quite often a patient may wish to repeat the entire course. Often, too, a patient will return in two or three years to repeat the sessions, feeling that he is losing his grip on the methods he tried to learn.

Discussion

The Effect of Previous Schooling in the Patient: Whether the patient has an eighth grade education or is a college graduate seems to make little difference with either the patient's receptiveness or the effectiveness of the therapy. We have some big business executives who were completely rehabilitated after having been totally incapacitated by emotionally induced illness. The more highly educated patient is usually more appreciative of and enthusiastic over the uniqueness of the therapy, but the person of lower educational attainments carries out the directives quite as well.

The Personality of the Doctor Is Still Important in the Therapy: It must not be assumed that direct personal interchange between patient and doctor becomes either unnecessary or unimportant in the audiovisual method presented herein. The doctor must be continually checking to see that the patient is absorbing the material properly; he may have to stress a point here and there; he may have to apply a point specifically to the patient's own life. To do this effectively the doctor must obviously know precisely what each audiovisual session contains and what it is that the patient is being subjected to on any particular day. The audiovisual sessions do most of the talking for him, but his personal force must still be evident to the patient. The doctor must make the patient feel that in the audiovisual sessions it is the doctor who is talking to him. The doctor, and his personal effectiveness, still play the dominant rôle in the final effect.

Results

In evaluating any kind of treatment for emotionally induced illness an important point must be remembered. It is that *any* form of treatment at all, from faith healing to surgery or liver injections, if accompanied by a fair degree of salesmanship, will improve 60% of such patients for two months. This immediate, nonspecific effect holds true also if the treatment is labeled "psychotherapy," such as the audiovisual technic herein described, *and* it holds true as well of traditional psychiatric methods.

Furthermore, it is always unwise for the clinician who is developing a form of treatment to evaluate his own results, and I do so here with the feeling that the figures have not been washed clean of all traces of prejudice.

Follow-ups are difficult. Patients may not return after therapy just as often because they are no better as because they are better.

Results were graded on these arbitrary criteria:

Good result: The patient felt well and did not need to see a doctor for a year following therapy.

Fair result: The patient accepted his diagnosis and did not go to a doctor for a year following therapy, and although he continued to have his symptoms to some degree he bore them well.

Poor result: The patient felt no better after therapy and continued to see doctors.

Two hundred consecutive patients treated by the audiovisual technic were graded and compared with a group of 159 patients treated by "substitution therapy" and another group of 60 patients treated by the "nerves plus sedatives" method.[1] By "substitution method" is meant the method by which 86% of all emotionally induced illness is now being treated, that is, to give the patient some organic explanation for his trouble and then os-

TABLE 1

Type of Therapy	No. of Patients	Cured %	Improved %	Unimproved %
Substitution therapy	159	8	24	68
Nerves plus sedatives	60	5	17	78
Audiovisual therapy	200	63	20	17

tensibly treat this alleged illness. The "nerves plus sedatives" method consists in telling the patient simply that he is free from physical disease, that it is "his nerves" that are at fault, and giving some sort of sedative for relief. All three groups were treated by the same physician.

The results of these three forms of therapy are given in table 1. Unfortunately, results of a similar group treated by traditional psychiatric methods are not available.

The effectiveness of the audiovisual technic over the methods commonly used in medical practice is apparent. A comparison of the results of the audiovisual technic with the results of traditional psychotherapy would not be fair to the latter, even though data were available. The psychiatrists are most often called upon to treat patients who belong in class two (above) who, although they constitute only about 15% of the total number of emotionally induced illness, account for most of the failures by any tried methods. The patients in class one, whom the psychiatrist is almost never called upon to treat, are readily helped by the audiovisual method and would doubtless respond also to good traditional psychotherapy.

The effectiveness of the audiovisual technic can probably be greatly increased through more expert additions and alterations to the present ma-

terial. It is hoped that in time others, more expert than the writer in this line, may bring about such changes so that the medical profession may have an increasingly practical tool for the treatment of the most common disease in our practice.

There is at least one thing the audiovisual technic accomplishes: it frees the overly busy physician from having to treat emotionally induced illness by the substitution technic. He can feel less of a charlatan, and his office time need no longer be absorbed by attempts at punitive psychotherapy. He can get a glowing feeling when the grateful (and previously exploited) patient tells him, "Doctor, this was wonderful; why didn't someone tell me this before?"

Summary

1. Emotionally induced illness is the greatest problem in contemporary medical practice, both because of its prevalence, and because prevailing methods of treatment are so poor.

2. Time is the big deterrent to the use of what is known as "adequate psychotherapy," and as a method it can never meet the present needs of general medical practice.

3. A method is presented of directive psychotherapy given to the patient by tape recordings, coupled with a slide projector.

4. Such a method of audiovisual presentation must necessarily diverge widely from current psychiatric methods and concepts.

5. The learning-maturity concept lends itself to audiovisual presentation. This concept is explained and the technic of its application developed.

6. The method gives the patient 15 hours of directive psychotherapy, and requires of the doctor no more time than is necessary for a thorough physical examination.

7. The results of the method are compared with the results of other forms of therapy commonly used for emotionally induced illness.

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CASE REPORTS

KAPOSI'S SARCOMA FOLLOWING ALLERGIC ANGIITIS *

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INTRODUCTION

KAPOSI'S sarcoma is an uncommon neoplastic lesion, usually of low grade malignancy, which is thought to be of vascular tissue origin. Most authors, including Algerter and Peale,[1] classify it as an angiosarcoma. The disease seems to have a predilection for Central European stock, affecting northern Italians most frequently, then Jews, Russians and Poles, in that order. The most common age of onset is in the fifth and sixth decades; males are the more frequent victims by a ratio of 20:1.

Kaposi's sarcoma has been reported frequently in association with malignancies of the lymphatic system, such as mycosis fungoides,[2, 3] lymphosarcoma,[4] Hodgkin's disease,[5, 6] and lymphatic leukemia,[7, 8, 9] as well as such varied conditions as myelogenous leukemia and hemolytic anemia.[10] Despite the fact that Kaposi's sarcoma in its early stages resembles a chronic inflammatory reaction, there is no reference in the literature to its occurrence following an acute allergic inflammation of the arterioles. The patient presented herewith, who has a familial history of the disease, developed Kaposi's sarcoma while undergoing corticosteroid therapy for acute angiitis.

CASE REPORT

This 53 year old white female of Italian descent was first admitted to the Long Island College Hospital on May 1, 1953, with the complaint of "bumps on the skin."

Approximately six months prior to admission the patient had developed a sharp, intermittent, nonradiating periumbilical pain, unrelated to meals or position, which was so severe as to awaken her from sleep. A physician administered an injection which relieved the pain; the patient was told that she had a viral infection. The same pain recurred a few weeks later and the patient received an injection of penicillin; the following morning she awakened with her face swollen and a brownish discoloration under both eyes. She was again seen by her physician, who made a diagnosis of "hives" and administered what was apparently an antihistaminic. The swelling subsided but recurred nine times during the next few weeks, and each time was treated by injection.

One month later the patient developed a diffuse pruritic, papulosquamous, erythematous rash on the chest, back, shoulders and thighs. She attended the Dermatology Clinic at the Long Island College Hospital, where she received calamine lotion with phenol, and antihistaminics, and was advised to take starch baths. The erythematous rash disappeared in a week. Several weeks later, however, the patient

* Received for publication May 3, 1954.
From the Department of Medicine, Long Island College Hospital.

was noted to have lentil-sized, violaceous, indolent nodules on the arms and legs, some of which were hyperpigmented. The diagnosis of Boeck's sarcoid was entertained, but biopsy of a violaceous skin nodule was reported as acute arteritis (figure 1). New violaceous nodules appeared on the face, forearms, legs and postauricular areas. Concurrently the patient noted an increased sensitivity to cold, manifested by blanching and a waxy appearance of the hands. The patient was then admitted to the Long Island College Hospital.

Family History: It was learned later that at the time of this patient's admission a maternal uncle was receiving radiation therapy for Kaposi's sarcoma.

Physical examination revealed a well developed, obese white female in no distress. The temperature was 100.2° F.; the radial pulse was 80 per minute; the respirations were 20 per minute. The blood pressure was 120/80 mm. of Hg in both

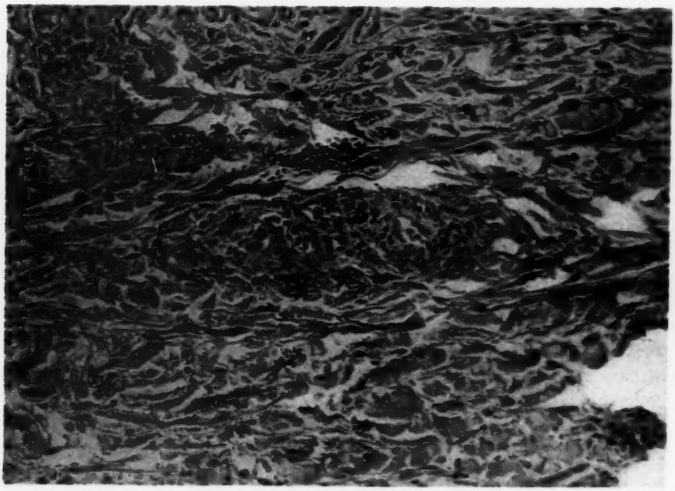

FIG. 1. There is a group of arterioles and capillaries in the dermis which are lined by swollen endothelial cells. The walls of these vessels as well as the tissue about them are infiltrated by polymorphonuclear leukocytes and lymphocytes. Hematoxylin and eosin stain. Magnification 400 ×.

arms. An erythematous, maculopapular rash was present over the malar areas of the face, over the medial aspect of the anterior chest, and the ventral aspect of the forearms. Violaceous nodules, from 3 mm. to 1 cm. in size, were noted over the forearms, neck, thighs and calves, and in the vaginal mucosa. The remainder of the skin was warm and moist. There were several discrete, hard, freely movable, nontender lymph glands in both submaxillary, submental and anterior cervical regions. The buccal mucosa was normal. The thyroid gland was not palpable, and the trachea was in the midline. The breasts were large and pendulous; the nipples were erect, and no masses or discharges were noted. The lungs were clear to percussion and auscultation, and diaphragmatic excursions were within normal limits. The apical impulse was in the fifth left interspace at the midclavicular line, and no thrills or murmurs were present. The rhythm was regular. The abdomen was soft and nontender; no organs or masses were palpable. The extremities showed no cyanosis, edema or clubbing. All the peripheral pulses were palpable, and skin temperatures

were normal to palpation. Rectal examination and proctoscopy to 20 cm. were negative. Vaginal speculum examination revealed the aforementioned violaceous nodules in the vaginal mucosa but was otherwise normal.

Laboratory Examinations: Blood hemoglobin, 10.6 gm./100 c.c.; red blood cells, 4,970,000; white blood cells, 9,550, with polymorphonuclears, 66%; lymphocytes, 25%; monocytes, 7%; eosinophils, 2%. Platelets, 232,000/mm³. Stained smear, microcytic, hypochromic erythrocytes; normal leukocytes and platelets. Bleeding time, 7 minutes; clotting time, 2 minutes. Rumpel-Leede test, positive. Reticulocytes, 4.9%. Erythrocyte sedimentation rate, 53 mm./hr. (Westergren). Hematocrit, 40%; eosinophils, 250/mm³. Mazzini (blood), negative. Lupus preparation, negative three times.

Chemical Tests: Fasting blood sugar, 94 mg./100 c.c.; urea nitrogen, 15 mg./100 c.c.; uric acid, 2.8 mg./100 c.c. Total protein, 7.0 gm./100 c.c.; serum albumin, 4.2; serum globulin, 2.8. Carbon dioxide combining power, 27.8 mEq./L. Chlorides, 100 mEq./L. Sodium, 134 mEq./L. Potassium, 5.4 mEq./L.

Urinalysis: Specific gravity, 1.020; pH, 5.6; color, amber; turbidity, clear; albumin, 0; acetone, 0; sugar, 0; microscopic: no casts or cells.

Bone marrow aspiration revealed an increase in mature eosinophils, but no tumor cells were seen.

An electrocardiogram was normal. An electroencephalogram showed a tendency toward cerebral dysrhythmia on hyperventilation.

A roentgenogram of the chest showed minimal cardiac enlargement, mainly left ventricular, and elongation of the aorta. Roentgenography of the abdomen showed minimal hepatic enlargement. Roentgen studies of the skull and hands revealed no abnormality.

While in the hospital the patient ran a low grade fever, usually about 100° F., but rising once to 102° F. The maculopapular rash cleared on antihistaminic therapy, but new violaceous nodules developed on the fingers of both hands.

A biopsy of a skin nodule during this admission was again reported as acute arteritis. A cervical lymph gland biopsy was reported as subacute lymphadenitis.

It was felt that this patient had developed an arteritis on an allergic basis, probably as an early manifestation of a collagen disease. On this assumption, cortisone therapy was instituted in a dosage of 25 mg. every six hours. This regimen of treatment failed to ameliorate her symptoms. She developed signs of hypocorticism and steroid therapy was discontinued.

The patient was discharged on May 18, 1953, to be followed in Clinic, but she failed to return to Clinic and discontinued her medication. Her symptoms persisted and after three months she returned. At this time cortisone therapy was instituted in the dosage of 100 mg. a day for one month. The cervical lymphadenopathy became more marked, and splenomegaly was noted for the first time. The cortisone was discontinued and therapy with Acthar-gel, 40 units a day, was instituted for one month. Axillary and inguinal lymphadenopathy appeared, and the patient noted that her Raynaud's phenomenon was more severe. She was re-admitted to the hospital on October 19, 1953, for further evaluation.

Examination at this time revealed new violaceous lesions on the forearms, as well as the previously mentioned lymphadenopathy and splenomegaly. A pigmented lesion from the right arm was biopsied and Kaposi's sarcoma was diagnosed (figure 2). The remainder of the laboratory data was the same as previously. Repeat biopsies of the skin of the thigh and of a cervical node were also diagnosed as Kaposi's sarcoma (figure 3). While in the hospital the patient ran a low grade fever up to 101° F. at night.

The patient received radiation therapy to the skin and lymph nodes, with slight improvement in her symptoms. However, the Raynaud's phenomenon became very

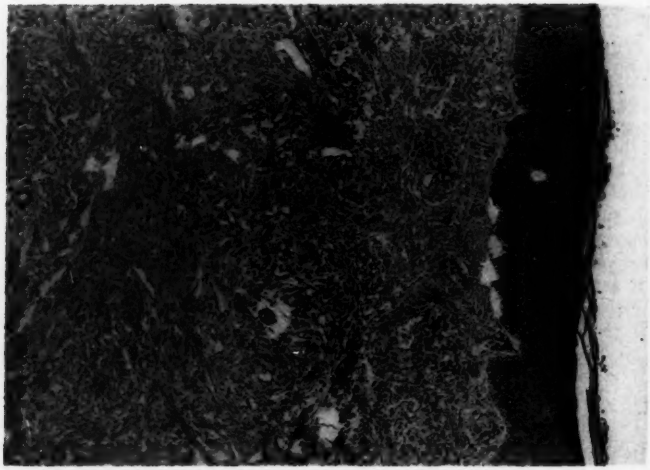

FIG. 2. In the dermis there are numerous small blood vessels which traverse the fibrous tissue in irregular fashion. The blood vessels are thick-walled and frequently comprised of multilayered spindle-shaped cells. The latter occur in groups between blood vessels. These spindle-shaped cells show nuclear enlargement and hyperchromatism. Scattered blood vessels contain numerous lymphocytes in their wall. Hematoxylin and eosin stain. Magnification 150 ×.

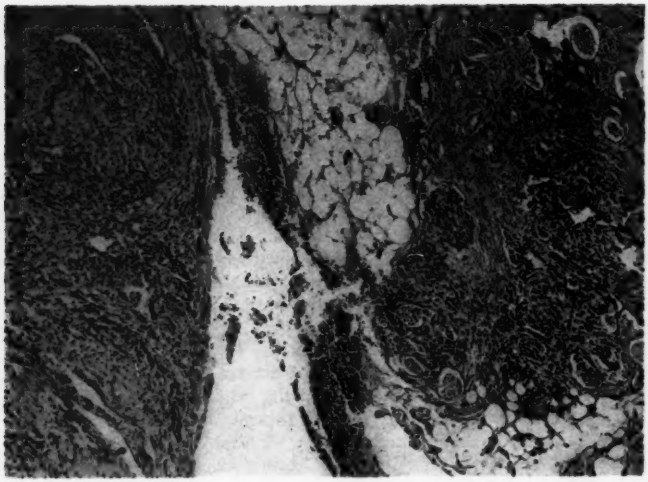

FIG. 3. Cervical lymph node showing virtually complete replacement of lymphoid tissue by groups of blood vessels. These show richly cellular walls comprised of small spindle-shaped cells. Similar cells occur in the supporting perivascular tissue. Hematoxylin and eosin stain. Magnification 150 ×.

severe, and treatment with Priscoline was instituted. The patient's symptoms responded well to this therapy, but syncope and nausea forced discontinuation of the drug.

She was discharged from the hospital on October 28, 1953, and has subsequently been observed in Clinic for several months, with no progression of her disease.

Description of Pathologic Lesions

The first biopsy of skin was taken from the right forearm on April 16, 1953. The skin lesions were described as being lentil-sized, infiltrated violaceous nodules on the arms and legs. Some lesions were noted to be hyperpigmented. Microscopically, the skin biopsy showed scattered groups of blood vessels in the dermis which demonstrated increased cellularity of their walls with polymorphonuclear leukocytic infiltration. Most of the involved blood vessels were of arteriole or precapillary caliber. These vessels were lined by plump endothelial cells (figure 1). The diagnosis made at this time was acute arteritis of skin.

On May 5, 1953, an additional skin biopsy and lymph node biopsy from the neck were taken. Microscopically, the skin showed infiltration of the blood vessels of the dermis with lymphocytes, eosinophils and a few plasma cells. These cells were most numerous about arterioles, but slight infiltration around veins was also present. The cervical lymph node showed diffuse hyperplasia of lymphoid and reticulum cells, with scattered foci of increased vascularization and fibroblastic proliferation in medullary sinuses. A diagnosis of acute arteritis of skin and subacute lymphadenitis was made.

The next biopsy of skin was performed on September 30, 1953, from a pigmented lesion of the right arm. The microscopic sections from a cutaneous nodule at this time showed the dermis to be traversed by numerous groups of small blood vessels. These occurred as clusters, sometimes grouped about sweat glands. The blood vessels were of capillary or arteriolar caliber and were lined by plump endothelial cells which sometimes were multilayered. The walls were thick, and in these as well as in the surrounding tissue large spindle-shaped fibroblasts were noted. These showed rare mitoses. Small to moderate numbers of lymphocytes and fewer eosinophils and plasma cells were present about some of the arterioles. The epidermis was intact overlying the nodule (figure 2). A diagnosis of Kaposi's disease of the skin was made at this time.

On October 27, 1953, an enlarged cervical lymph node was removed. Sections disclosed a group of small lymph nodes. Microscopically, portions of the nodes were replaced by groups of blood vessels of varied caliber and appearance (figure 3). Most of the blood vessels showed cellular thickened walls and were grouped as clusters. The lining endothelial cells were enlarged and multilayered. Elsewhere the lymph nodes showed areas of fibrosis as well as foci of reticulum cell hyperplasia. A diagnosis of Kaposi's disease of cervical lymph node was made.

Discussion

The etiology and pathogenesis of Kaposi's sarcoma have been in dispute [11, 12] ever since its description 82 years ago. The pigment deposition, hemorrhagic tendencies and round cell infiltrations led earlier investigators to describe it as inflammatory in nature. It continued for many years to be considered a chronic, smoldering, inflammatory process. However, the neoplastic proclivities of the later lesions have now swung the majority toward considering it a low grade malignancy. Dorffel,[13] in reporting his series of cases, described the lesion as being initially inflammatory. Ormsby and Montgomery [14] perhaps stated the

correct sequence of events when they postulated that some toxic or infectious substance acts on the vascular system; this causes an inflammatory reaction which, in time, leads to a true proliferation of the cells of the small blood vessel walls. Algerter and Peale [1] feel that endothelial hyperplasia is an important factor in the early pathogenesis of Kaposi's sarcoma. MacKee and Apollara,[15] on the other hand, feel that some unidentified toxin produces an inflammatory state ". . . indistinguishable from neoplasia." Most authors are agreed that the entire Kaposi's syndrome begins as a chronic inflammation of the small arteries which, at some point, blends into a low grade neoplasm with malignant potentialities. In the case presented, a patient in seeming good health progressed through an acute vascular inflammation (as evidenced by a penicillin reaction) to a classic Kaposi's sarcoma. No evidence of Kaposi lesions was noted until the allergic dermatitis was on the wane; the first violaceous nodule biopsied showed only an angiitis (figure 1). Indeed, there was no reason to suspect anything but a "serum sickness" until the nodules began to appear in great numbers. Raynaud's phenomenon developed at the same time as the nodular lesions.

In view of this sequence of events, it seems reasonable to suggest that in this case the original lesion was an angiitis due to penicillin sensitivity, which evidently progressed to the characteristic malignant lesions of Kaposi's sarcoma. It is interesting to note that corticosteroid and corticotrophin therapy seemed to enhance the progression of the lesions. The authors could find no references in the literature concerning the possible inciting role of these hormones in the development of malignancy. There is not sufficient evidence to incriminate them here; the importance of their role is certainly open to speculation. Raynaud's phenomenon is not a concomitant of either allergic arteritis or Kaposi's sarcoma. In this patient the syndrome developed at the height of her sensitivity reaction. It became worse as the Kaposi lesions made their appearance. The literature records no previous occurrences of Raynaud's phenomenon with either Kaposi's sarcoma or allergic angiitis.[16, 17]

The case presented is of unusual interest in that a patient with a vascular inflammation of known etiology was closely followed as she developed a vascular sarcoma. This sequence seems to justify the classic concept of the pathogenesis of Kaposi's sarcoma.

Summary

A case is presented in which Kaposi's sarcoma developed in the course of an allergic arteritis.

Acknowledgment

The authors wish to express their appreciation to Dr. Thomas Morrione, Director of Pathology at the Long Island College Hospital, for the gross and microscopic descriptions of the lesions and the legends of the photomicrographs.

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IMPAIRED GLUCOSE TOLERANCE, A CONSEQUENCE OF EXCESSIVE CARBOHYDRATE CONSUMPTION *

By Samuel Alpert, M.D., *New York, N. Y.*

Despite intensive investigative work, diabetes mellitus remains a disorder of unknown etiology whose clinical manifestations constitute a symptom complex composed of impaired glucose tolerance, neuropathy, nephropathy, retinopathy and accelerated atherosclerosis. The site of the anatomic defect remains obscure. There is no indication that the primary basic pathology is wholly confined to the pancreas, nor is there evidence that excessive carbohydrate consumption is in any way related to the development of the disorder. On the other hand, any primary affliction of the pancreas may give rise to carbohydrate disturbances indistinguish-

* Received for publication April 29, 1954.
From the Veterans Administration, New York Regional Office.

able from that seen in true diabetes mellitus by reason of diminished production of insulin. Such affliction may be the result of inflammatory or neoplastic disease, or surgical ablation. A rather uncommon cause for reduced insulin synthesis is exhaustion of the islet tissue by excessive functional demand, a consequence of excessive carbohydrate intake. The following case represents the second report[1] in recent months of such a phenomenon.

Case Report

A 19 year old white male, inducted into service January, 1945, was admitted to an Army hospital in January, 1946, complaining of abdominal pain of several hours' duration. In the course of the routine work-up glycosuria and acetonuria were discovered. The abdominal pain, the etiology of which was obscure, subsequently subsided. There was no history of polydipsia, polyuria or decline in weight. The patient stated that he had always been fond of sweets, which were in short supply for him in civilian life. In the military service he indulged his craving quite liberally with the adequate supplies at the post exchange. His daily consumption averaged 24 bars of chocolate candy, two to three glasses of malted milk, and several bottles of soda pop, all in addition to three generous meals. Despite this gluttony his weight remained at a level of 170 pounds, about average for his height of 72 inches. There was no family history of diabetes. The initial blood sugar was 140 mg. %. No glucose tolerance test was done at the time. The patient was placed on a dietary régime (carbohydrates, 200; protein, 95; fat, 75) and given insulin. His course in the hospital was one of progressive improvement. Insulin needs gradually decreased from 40 to 15 units of protamine zinc insulin. The fasting blood sugars fluctuated between 125 mg. % and 135 mg. %. He was separated from the service in June, 1946, because of this diabetic state, and remained on the prescribed régime for about six months, at the end of which time insulin was withdrawn because of persistent aglycosuria. He was first seen at the New York Regional Office for routine check-up in 1947. Physical examination was completely negative. There was no clinical evidence of hyperthyroidism, and the basal metabolic rate was normal. A standard oral glucose tolerance test revealed the following figures: fasting, 142 mg. %; one-half hour, 165 mg. %; one hour, 197 mg. %; two hours, 167 mg. %; three hours, 145 mg. %. There was a minimal spill of glucose in the last three specimens of urine. The weight at the time of this examination was 165 pounds, five pounds below his usual level. A repeat tolerance test done one year later, in April, 1949, revealed the following figures: fasting, 113.5 mg. %; one-half hour, 148 mg. %; one hour, 129 mg. %; two hours, 120 mg. %; three hours, 107 mg. %. Since this curve reflected normal tolerance, the diagnosis of diabetes mellitus was withdrawn and the patient so informed. He promptly resumed his old gluttonous habits, which he maintained until his next visit to the clinic in May, 1951. It was estimated at that time that his daily intake in this interval had been approximately 7,000 calories of which 4,000 calories were derived from carbohydrate sources. Despite the magnitude of this intake his weight showed no change. A glucose tolerance test gave the following figures: fasting, 175 mg.%; one-half hour, 208 mg. %; one hour, 208 mg. %; two hours, 242 mg. %; three hours, 229 mg. %, with a urinary spill of 0.45%, 0.7% and 0.45% glucose in the third, fourth and fifth specimens, respectively. When questioned about the reason for his dietary habits the patient indicated that he was constantly hungry and that his failure to appease his hunger made him very uncomfortable and evoked a feeling of numbness in his hands, feet and lips. The relationship of the excessive intake to his diminished tolerance was pointed out to him, and a new dietary scheme (carbohydrates, 250; protein, 115; fat, 90) was prescribed. After two months of this régime a glucose tolerance test on July 15, 1951, gave the following results:

fasting, 132 mg. %; one-half hour, 166 mg. %; one hour, 185 mg. %; two hours, 160 mg. %; three hours, 148 mg. %, with a very minimal spill in the last three specimens of urine. In October, 1951, a repeat glucose tolerance test continued to reveal mildly impaired tolerance: fasting, 134 mg. %; one-half hour, 203 mg. %; one hour, 195 mg. %; two hours, 133 mg. %; three hours, 114 mg. %; four hours, 119 mg. %. In April, 1952, after 11 months of a régime of restricted dietary intake, a third tolerance test revealed the following curve: fasting, 120 mg. %; one-half hour, 136 mg. %; one hour, 106 mg. %; two hours, 108 mg. %; three hours, 109 mg. %. His weight at the time was 172 pounds, essentially unchanged from the level of the year before. There was no further contact with the patient after this date. The forementioned data are tabulated below:

Glucose Tolerance in Relation to Food Intake

Dietary Habits		Blood Glucose Determination in Mg. % (Folin-Wu)					
Time Range	Food Intake	Date	Fasting	½ Hr.	1 Hr.	2 Hrs.	3 Hrs.
Jan. 1945 thru 1946	Excessive	1946	140				
Jan. 1946	Restricted	Dec. 1947	142	165	197	167	145
Apr. 1949		Apr. 1949	113.5	148	129	120	107
Apr. 1949 May 1951	Excessive	May 1951	175	208	208	212	229
May 1951	Restricted	July 1951	132	166	185	160	148
		Oct. 1951	134	203	195	133	114
Apr. 1952		Apr. 1952	120	136	106	108	109

Discussion

The impairment of glucose tolerance following ingestion of an excessive amount of carbohydrates is graphically depicted here. Recovery of normal function, though it lagged, definitely followed the adoption of restrained dietary habits.

A plausible explanation of the phenomenon may be offered based on data accumulated in the laboratory on experimental diabetes. Since Homans' initial work in 1914 [2-7] it has been repeatedly demonstrated that hyperglycemia is an important factor in the development of lesions of the islet tissue of the pancreas clinically manifested by impaired glucose tolerance. Such lesions may vary from degranulation to hydropic degeneration to complete atrophy. If the changes do not extend beyond the stage of hydropic degeneration they are reversible, provided the provoking factor is removed. Various methods have been employed to induce the hyperglycemic state. Daily injections of crude anterior pituitary extract (which probably operates by its inhibitory action on effectiveness of insulin) and high carbohydrate feeding, given parenterally either by the intravenous or intraperitoneal routes, have been the methods most commonly used. Factors which tended to lower the blood sugar, such as insulin, phlorhizin, fasting or high fat feeding, were protective against development of these lesions, or effected recovery if the damage had not progressed beyond an irreversible state.[8,9] It is generally accepted that the mechanism for such damage is functional overstimulation of the islet tissue through excessive demand for insulin. Where this de-

mand is maintained, exhaustion develops, reflected anatomically by degranulation. (The opinion of some investigators is that the granules represent insulin precursors.) If the overstimulation continues, ultimately irreversible changes in the form of complete degeneration and atrophy ensue, giving rise to a permanent impairment of glucose tolerance.

The work of Anderson and Long [10] with the isolated rat pancreas lends support to this hypothesis. They demonstrated that the amount of insulin recovered in washings was related to the level of glucose in the blood perfused through the organ. A perfusate of high concentration stimulated insulin secretion, while one of low concentration depressed it. In short, this was convincing proof that islet function was intimately related to the level of glucose in the blood stream.

Thus it can be postulated in this case that the disturbance of glucose metabolism was the result of islet exhaustion, induced by excessive consumption of carbohydrates. The capacity to maintain a normal level of blood sugar was repeatedly overwhelmed by rapid absorption of large amounts of glucose from the intestinal tract, causing a recurrent hyperglycemic state. This in turn gave rise to degenerative change in the pancreas, which presumably did not go beyond the state of degranulation, since reversibility of the clinical pictures was twice demonstrated.

The reason for the low functional reserve of the islet tissue is not apparent. Diminished carbohydrate tolerance has been noted in both endocrine and infectious disorders. The mechanism for impairment in such cases is not quite clear, but it presumably operates through interference with insulin effectiveness. However, such factors were not demonstrable in the case described here. One might therefore suggest a constitutional factor as responsible for the inherently low functional reserve.

It is to be emphasized that this case cannot be regarded as a true example of diabetes mellitus, nor can its development be regarded as in any way related to the pathogenesis of that disease.

Summary

1. A case of transient impairment of glucose tolerance resulting from excessive carbohydrate intake is presented.

2. The phenomenon is regarded as one of exhaustion of pancreatic islet tissue arising from excessive functional demand.

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CHYLURIA: CASE REPORT AND REVIEW OF LITERATURE*

By Dewey W. Johnston, M.D., *McKinney, Texas*

It has been about a century since chyluria was first recognized and its significance appreciated. The disease has been uncommon in this country. The exact pathogenesis is obscure. No satisfactory definitive therapy has yet been found. The following case is one of chyluria of parasitic origin.

Case Report

History: A 40 year old white male veteran was admitted to this hospital for the first and only time in November, 1952. He gave a history of a febrile illness associated with vomiting, malaise and bilateral orchitis while serving in the China-Burma-India Theatre in 1943. Shortly thereafter he was told he had filariasis. He gave no history of specific therapy. One year after this acute illness he noticed that the urine appeared milky. A tentative diagnosis of renal tuberculosis was made, and he was returned to the United States. Further study resulted in the diagnosis of chyluria; that of renal tuberculosis was not substantiated. In 1944 he developed nausea, vomiting, hematemesis and tarry stools. A subtotal gastrectomy or gastrojejunostomy was performed for peptic ulcer. Three months later hematemesis and tarry stools recurred, and resection of a stomal ulcer was carried out. In the meantime, chyluria continued intermittently. He said he passed "chyle" in the feces, and "chyle" was occasionally noted in the vomitus.

In 1945 he first noticed hematuria, which was present only at times when chyle was passed in the urine. The hematuria was associated with renal colic resulting from passage of clots consisting of chyle or blood or varying mixtures of chyle and blood. A right nephrectomy was performed at one hospital on the assumption that the hematuria was unilateral. The hematuria continued, and because it was thought that blood was coming from the ureteral stump a second operation was performed, removing the stump. Frequent episodes of infection of the urinary tract had occurred both prior and subsequent to nephrectomy. He continued to have massive hematochyluria and recurrent pyelonephritis. Cystoscopy was occasionally required for removal of large clots which obstructed the ureter.

In 1947 emergency splenectomy was performed for spontaneous rupture of the spleen. He recovered without sequelae. In 1948 surgery was performed because

* Received for publication April 27, 1954.
From the Veterans Administration Hospital, McKinney, Texas, and Southwestern Medical School of The University of Texas, Dallas, Texas.

of intestinal obstruction. Subsequently he developed a gastrojejunocolic fistula. During attempted repair of this defect he developed cardiac arrest, following which surgery was terminated without repair of the fistula. A previous cardiac arrest had occurred during the nephrectomy in 1945. Both of these episodes necessitated direct cardiac massage.

He apparently had required repeated transfusions during the past two to three years. He told of receiving as many as 40 to 50 pints of blood in a three month period. There was no history of purpura or of a tendency to bleed easily. Blood loss was by way of the urinary and gastrointestinal tracts.

Prior to his admission to this hospital, hematochyluria, renal colic and fever had become persistent. A 47 pound weight loss was recorded within a six week period. Diarrhea was marked. Stools were large, bulky, foamy and foul-smelling, and tended to float.

Physical Examination: Temperature was 100° F. orally; blood pressure, 120/80 mm. of Hg; pulse, 90/min.; respiration, 16/min. The patient was a tall, active individual with evidence of marked weight loss. The tongue was red and sore. The oral mucous membranes were hyperemic. Small ulcerations and exudate were noted over gums and palate. Cheilosis was present. There was no purpura. The ocular fundi were normal. The lung fields were clear. The heart was normal. The abdomen was tense, rigid and criss-crossed with scars from various operative incisions. There was marked costovertebral angle tenderness on the left. Slight nonpitting edema of the lower extremities was present. Palmar erythema was very prominent. Neurologic examination was normal.

Laboratory: Urinalysis revealed a specific gravity of 1.022 and 4 plus albumin. The urine was loaded with white blood cells in clumps, and red blood cells. The white count was 11,950. The differential was normal. Hemoglobin was 14.4 gm. %. Platelet count was 72,000. Bleeding time was 5½ minutes; coagulation time was 5 minutes. Clot retraction was good within one hour, and no lysis was noted. The Rumpel-Leede test for capillary fragility was normal. Prothrombin time was 70% of normal. Prothrombin consumption was 90%. Thromboplastinogen activity test was within normal limits. The direct and indirect Coombs' test was negative. Total cholesterol was 224 mg. %, with ester fraction of 147 mg. %. Total protein was 6.9 gm. %, with albumin of 4.8 gm. %. Blood urea nitrogen was 15 mg. %. Thymol turbidity was one unit. Bromsulphalein excretion showed 4% of dye retained at the end of 45 minutes. An electrocardiogram was normal. Chest x-ray was negative for significant abnormality. A gastrointestinal series showed no evidence of gastric or jejunal ulcer, and it failed to reveal a gastrojejunocolic fistula. Excretory urogram demonstrated a normal but hypertrophied left kidney. No pyelolymphatic back flow was noted.

Hospital Course: The hospital course was characterized by repeated bouts of renal colic, with passage of as many as 50 blood clots per day. Blood casts of the entire ureter as seen in the photograph were frequently passed. Octin and meperidine had to be given at frequent intervals. The hematochyluria failed to respond to low fat diet, bed-rest or changes in position. Repeated bouts of pyelonephritis occurred, the causative organism being *Aerobacter aerogenes.* No intermittence of his disease was noted during his hospital stay of five weeks. One renal calculus consisting of calcium carbonate and phosphate was passed. The presence of a gastrojejunocolic fistula was suspected when charcoal given orally appeared in the feces within 23 minutes. He continued to pass loose, watery stools containing undigested meat fibers and vegetable material; the stools did not appear grossly fatty. The patient was maintained on a low fat diet. Fecal vomiting developed, and continued to be a therapeutic challenge toward the latter part of his hospital stay.

Filariae were not demonstrated in blood or urine. There was no chyloascites or chylothorax. When butter stained with Sudan red III was administered orally,

it appeared in large amounts in the urine. The dye was extractable with ether along with the chyle. Hyaluronidase was given to determine its effect on clotting of chyle or blood within the ureter. Depoheparin was given in an effort to reduce the degree of chyluria, but in doses insufficient to affect clotting mechanism.

A bleeding abnormality was never demonstrated. Platelet counts were low but were never at a critical level. No decline in hemoglobin occurred during his seven week hospital course.

Review of Literature

The historical aspects of chyluria have been reviewed by others.[1, 2] The observation of oily or milky urine dates back to the writings of Hippocrates. It was only after Jean Pecquet discovered the circulation of lymph in 1651 that it was recognized that milky urine was produced by the presence of chyle in the urine. Only later, however, was the distinction between pyuria and chyluria clarified. The first recorded case of chyluria was published in 1812. In 1866 Wücherer demonstrated microfilariae in blood and urine in cases of chyluria. Since that time it has been recognized that the most common cause of chyluria is filariasis. Later in the 19th century extensive lymphangiectasis and fistulous tracts between the lymphatic and urinary system were demonstrated in subjects with chyluria. Recent advances include the observation of Hampton and others on pyelolymphatic backflow.[3, 4, 5] Although there has been some disagreement as to its importance, this mechanism has recently been emphasized by Japanese workers.[6]

The etiologic classification of chyluria is customarily considered under two categories, parasitic and non-parasitic.[7]

Parasitic:
1. Filariasis
2. Echinococcus
3. *Cysticercus cellulosae*
4. *Ascaris lumbricoides*
5. Malarial
6. Tinea vera

Nonparasitic:
1. Lymphatic aneurysm
2. Thoracic duct obstruction
   a. Trauma
   b. Tuberculosis
   c. Abscess
   d. Neoplasm

Evidence for parasitic causes of chyluria other than filariasis is very tenuous, and case reports are rare and poorly documented. Approximately 100 cases of "nonparasitic" chyluria have been reported in this country. Reports from Germany between 1850 and 1925 indicate that the "nonparasitic" type was not too uncommon in that country.

Parasitic chyluria is not at all uncommon in India. Ray and Rao [8] collected a series of 254 cases of chyluria occurring in a total of 12,386 individuals with filariasis, giving an incidence of 2% in all patients with filariasis. Geographic location is of importance in that the type of filariasis seen in the South Pacific,

Northern Japan and China is not accompanied by the high frequency of chyluria reported in Southern China, Burma and Northern India.

It is approximately nine times more common in men than in women. The age of onset is earlier in the female. The disease has been noted in individuals of varying age groups ranging from 17 months to 70 years.

There are two theories pertaining to the origin of chyle in the urine, the secretory theory and the mechanical theory.[8, 9, 10] Proutz and Goetz in 1841 postulated that the chyluria resulted merely from "leakage" of chyle through the glomerular epithelium. There have been no direct data to support this concept, and it is inconsistent with the intermittent and asymmetric manifestations frequently observed in this disease. The accepted theory is that first proposed by Ackerman and Van Dyke Carter. It assumes blockage of lymphatics with increasing "back pressure." The valves of the lymphatics dilate, forming extensive lymph varices. Rupture of a varix results in the development of a lymphatico-urinary fistula and the flow of lymph or chyle into the renal pelvis, ureter or bladder.

A further feature of the mechanical theory concerns the concept of pyelolymphatic backflow, with a direct communication between lymphatics and urinary tract at the fornix or the fornices of minor calyces.[11, 12] There remains no doubt that lymphatic obstruction is a major factor, however. Several authors have emphasized the relationship of pyelolymphatic backflow to chyluria.[5, 6, 13]

Yamauchi has demonstrated pyelolymphatic backflow in individuals exposed to filariasis in the absence of chyluria in a significantly greater percentage than is seen in normals.[6] This phenomenon was observed without increasing intrapelvic pressure. He noted pyelolymphatic backflow during intravenous urography in 24 of 32 cases of chyluria. Associated renal infection has been stressed as a chief precipitating, aggravating or perpetuating factor. Yamauchi considers pyelonephritis almost universal in chyluria. Finally, dilated lymphatics may rupture into the intestinal tract, the pleural and peritoneal cavity and into the pericardial sac.

The hematuria which so frequently accompanies chyluria is assumed to be associated with rupture of minute blood vessels adjacent to the site of fistula formation.

The chief symptom is the passage of "milky urine," with or without the presence of blood. The material may coalesce into ureteral casts, and renal colic may be severe and unrelenting. Intermittence is highly characteristic. Hematuria may be the presenting symptom. Chyluria and hematuria may be unilateral. Urinary tract infection is present in the vast majority of cases. The gastrointestinal symptoms may be nondescript in character or may simulate the sprue syndrome. Malnutrition is a common feature, and is usually greater than can be accounted for by the calories lost in the urine. Avitaminosis may be present. The skin is tough and rubbery and often assumes a dull, dusky, dirty pallor.

Fatty meals are not well tolerated. Severe chyluria may persist despite an extremely low fat diet. The recumbent position may alleviate symptoms of chyluria in some individuals, and exertion is occasionally a prominent aggravating factor. Pregnancy and menstruation have been noted to be precipitating factors.

The urine in such patients may look like cream. The fat content varies between .2 and 4%, and fat globules may be seen floating on the surface. The colloidal suspension of chyle will not separate on centrifuging. When the urine has

been standing, three layers are usually seen: (1) a top layer of fatty material; (2) a middle pinkish layer, often containing a clot; (3) a bottom layer of blood and débris. Chyle will dissolve in ether when mixed with urine in ratio of 1:1. Protein, albumin and fibrinogen are found in the urine. Pyuria and varying degrees of hematuria are usually present. Microfilariae can be observed in the urine for a period of about six weeks after an acute infection. Thereafter they are usually not discovered unless the individual has remained in an endemic area.

A simple test for the confirmation of chyle in the urine consists of administration of 100 mg. of Sundan red III mixed with 10 gm. of butter, which can be eaten on bread or toast. Urine is collected for period of two to four hours thereafter. In cases of chyluria the urine appears bright orange, due to the staining of fat particles with Sudan red III. The dye-stained chyle can be extracted with ether. Sudan red III will not appear in the urine of normal individuals.

The differential diagnoses that might be entertained are those conditions in which fat can be found in the urine.[15] Lipiduria may be noted in association with fat embolism. Fat may be seen in the urine of nephritis and in the nephropathy of diabetes. Degenerating tumors of the kidney may cause fatty material to appear in the urine. Certain nephrotoxins, notably phosphorus, may produce fat in the urine.

The therapy of chyluria has been rather unsatisfactory. Antifilarial drugs are useless except during the acute phase of filariasis. One of the most effective means of therapy consists of intrapelvic instillation of 1 to 3% silver nitrate.[14] If fistulous openings can be observed through the cystoscope, fulguration of this site is often effective.[2] A low-fat diet, bed-rest and recumbent posture are simple measures which may be of great benefit. Although nephrectomy has been done when the disease is unilateral, it is not recommended.[2] Decapsulation and removal of perirenal lymph channels and nodes have no place in the therapy of chyluria.[15] Renal infection should be investigated and treated with the antibiotics most effective against the causative organism.

Discussion Of Case

The febrile illness this patient had in 1943 was diagnosed as acute filariasis. No history of specific therapy was obtained. A latent period of one year was noted before development of chyluria. The intermittence of the symptoms seen in this disorder is well exemplified in this case. The longest period of continuous symptoms had been two months, and this was during his admission to this hospital. During remissions he would gain as much as 50 pounds and was able to eat one pound of butter and one quart of cream a day without recurrence of symptoms. In fact, it was customary for him to do just that in order to regain strength and weight rapidly. No explanation for his intermittent course was found. No remission occurred prior to his release from the hospital. Rest and posture had no effect on the severity of the chyluria. Temperature elevation was intermittent throughout the course, usually being low grade, with occasional peaks as high as 103° F. Fever is said to be a feature of chyluria. It may be related to bouts of pyelonephritis, as it seemed to be in this patient. Bacterial flora in the urine varied, but the outstanding pathogen was *B. proteus*, which was resistant to all available antibiotics and clinically resistant to combinations of drugs. Despite his having this persistent and rather severe pyelonephritis and

previous nephrectomy, renal excretory function was normal. Hypertension was not present. Ureteral casts of pencil-sized diameter (figure 1) were passed frequently. Hyaluronidase intramuscularly was tried in the hope that from its effect on colloids in the urine less tendency for clotting would result. No effect was noted. Heparin was tried intramuscularly in rather small doses in an effort to affect the suspension of chylomicrons. Again, no effect was seen. Complete obstruction due to ureteral casts was suspected on several occasions. The duration was never longer than eight hours. Relief was accomplished by conservative measures, and cystoscopy was not required.

The gastrointestinal symptoms were outstanding and in many respects simulated the picture of sprue. The picture in this case was, however, complicated by a gastrojejunocolic fistula manifested by severe diarrhea (charcoal given orally passed in 23 minutes) and fecal vomiting. An interesting historical point was that of having vomited "chyle." This was never objectively verified. The patient had noted this only when chyluria was present. It is conceivable that

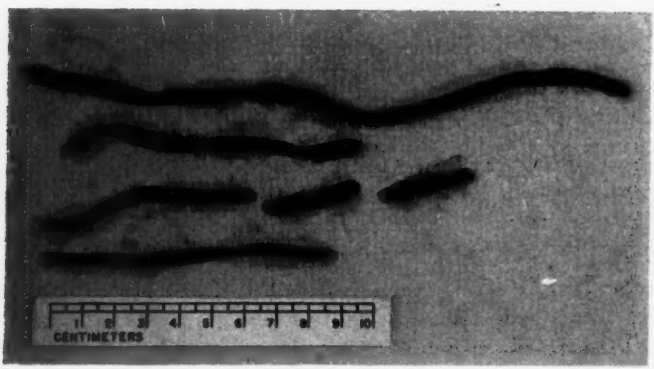

FIG. 1. Ureteral casts of clotted blood from one urine specimen.

chylo-enteric fistulae could exist and give rise to this symptom. That chyle abscesses within the enteric wall and their subsequent intraluminal rupture were the pathogenesis of the previous "peptic ulcer" and subsequent "stomal ulcer" does not seem remote.

The character of his skin was most unusual. Its toughness and rubbery feel were repeatedly commented upon by the individuals who gave him injections. Many needles were bent attempting to give him intramuscular injections. Subcutaneous and intramuscular absorption of drugs was interfered with because the medication would repeatedly drain from sinus tracts produced by the needle.

The failure of nephrectomy as therapy for unilateral hematochyluria is well exemplified in this patient. He had had temporary relief early in his course with the use of silver nitrate lavage of the renal pelvis. Octin was demonstrated to be an excellent spasmolytic agent for the ureter. He would not tolerate an enteric tube which was passed in attempt to by-pass the fistula. High colonic irrigation with continuous suction failed to affect significantly the fecal vomiting. His course was unchanged while in this hospital. He was released unimproved after hospitalization of five weeks.

SUMMARY

A case of chyluria secondary to filariasis has been reported. The English literature has been reviewed.

ADDENDUM

This patient was seen again 15 months later (in March, 1954), at which time his condition was essentially unchanged except that his nutrition had improved and his weight was 20 pounds more than previously. His course had been characterized by periods of remission lasting months, and he had gained a maximum of 40 pounds during remissions. He told of the removal of a "chyle abscess" within the abdomen one year ago. Fecal vomiting, a tendency toward avitaminosis and intermittent hematochyluria continue.

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RECURRENT HEART FAILURE WITH TAMPONADE DUE TO PERICARDIAL EFFUSION; IMPROVEMENT FOLLOWING PLEURAL–PERICARDIAL FENESTRATION *

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THE management of heart failure due to pericardial effusion involves two general phases. When cardiac tamponade is the pressing problem, the patient

* Received for publication May 14, 1954.
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can be immediately benefited by a pericardial tap, which also affords diagnostic data. Otherwise treatment is directed at the underlying cause, be it inflammatory, traumatic, neoplastic, nutritional or metabolic, in an attempt to prevent re-accumulation of fluid. While this regimen usually suffices, an occasional instance will arise where repeated re-accumulation of fluid cannot be controlled in this way. The outlook then becomes unfavorable unless another means can be devised to prevent cardiac tamponade, with its attendant diminished cardiac output and congestive failure. This report describes a new procedure for the management of severe tamponade due to recurring pericardial effusion.

Case Report

The patient, a white married housewife, had had measles, scarlet fever, chicken pox and a tonsillectomy in childhood. Her menses began when she was 17, and an appendectomy was performed at the age of 21. A normal pregnancy occurred at the age of 23 in 1938. The family history was noncontributory. In 1939 the patient developed nervousness, restlessness, irritability, sweating, insomnia, diarrhea and weight loss. Slight exophthalmos was present. The basal metabolic rate was within normal limits. Following thyroidectomy in September, 1939, the patient suffered from fever for a few days and drainage from the operative site for six weeks. Although the exophthalmos receded, nervousness continued and her menses were unchanged. The skin became dry and coarse, and occasional episodes of cramping abdominal pain occurred. She was treated with 16 mg. to 60 mg. of thyroid extract daily.

In 1945 the patient was first hospitalized at Kings County Hospital because of cardiac tamponade. Examination revealed weakness, orthopnea, dyspnea, cyanosis and left chest pain. Her skin was coarse, dry and a pale gray-brown in color; eyebrow, head and axillary hair was coarse and scanty. Hypersensitivity was noted to cold exposure; her menses were irregular and infrequent. On physical examination the blood pressure was 120/100 mm. Hg; pulse, 98 and regular; temperature was normal; the heart sounds were distant, and the peripheral veins were distended. The circulation time (Decholin) was 22 seconds; venous pressure (antecubital) was 240 mm. H_2O; the basal metabolic rate varied from minus 26% to $\pm$ 1%; total serum cholesterol, 238 mg. %; sedimentation rate, 24 mm./40 minutes; upper and lower gastrointestinal and gall-bladder x-ray series were negative. The hemogram, urinalysis, serology and blood chemistry determinations, including a glucose tolerance test, were normal. An electrocardiogram revealed low QRS voltages and flattened T waves; an x-ray of the chest showed a water-bottle configuration of the heart with an increased transverse diameter; bilateral small pleural effusions were present. Three hundred cubic centimeters of clear, straw-colored fluid were removed from the left pleural cavity, and 600 c.c. of fluid were removed from the pericardium. Air was injected into the pericardium. Subsequent x-rays revealed a pneumohydropericardium with marked diminution of the heart size; there was no evidence of pericardial thickening. Smears and cultures of the sputum, pericardial and pleural fluids were negative for acid-fast organisms. Following the pericardial tap the venous pressure fell to 40 mm. of water and the circulation time to 10 seconds; the sedimentation rate became normal. The patient was discharged and continued on 45 mg. of thyroid extract daily. The diagnosis was myxedema with pericardial effusion. Larger doses of thyroid extract caused itching and crampy abdominal pain.

She was followed during the next year in the outpatient department, where her clinical picture remained that of hypothyroidism despite gradual increase in thyroid extract to 300 mg. daily. The basal metabolic rates varied from minus 17% to plus 1%. Progressive, generalized increase in the cardiac silhouette toward a water-

bottle shape with a widened base occurred; the lung fields became passively congested. Weekly injections of a mercurial (mercupurin, 2 c.c. intravenously) resulted in a diuresis but failed to control the recurring pericardial effusion. The patient was again hospitalized for cardiac tamponade accompanied by ascites in 1946. Marked clinical improvement followed a pericardial tap with the removal of a total of 1,400 c.c. of straw-colored fluid having a specific gravity of 1.025; it did not coagulate. Pneumopericardium was induced after the tap, and x-ray examination again revealed no thickening of the pericardium; the size of the heart was within normal limits, and the esophagram was normal. A culture and inoculation of a guinea pig with pericardial fluid remained negative for tubercle bacilli. After her discharge to the outpatient department, tamponade recurred despite 360 mg. of thyroid extract daily, mercurial diuretics, and a basal metabolic rate within normal limits. Five months later (1947) the patient was again hospitalized with severe tamponade which had

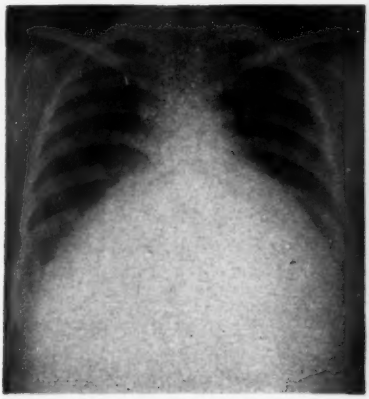

FIG. 1.

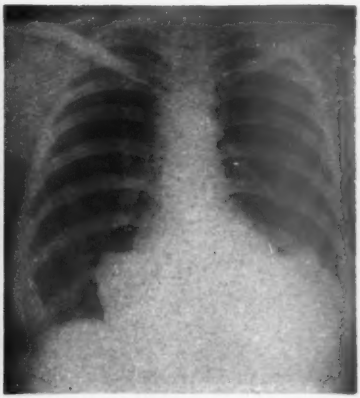

FIG. 2.

FIG. 1. Postero-anterior x-ray of chest, third hospital admission, 1947, showing pericardial effusion.

FIG. 2. Postero-anterior x-ray of chest after tap, showing pneumohydropericardium with fluid level, outlines of the pericardium and cardiac borders.

possibly been aggravated by previous withdrawal from all thyroid extract for three weeks because of rash and pruritus. Figure 1 is a teleroentgenogram of the chest showing the pericardial effusion on this, the third hospital admission. The skin cleared while thyroid medication was interrupted. Her hospital course was similar to that of previous admissions, the pleural effusion and pericardial collection, ascites and dyspnea responding only after the removal of 900 c.c. of clear fluid from the pericardium. Figure 2 is a posterior-anterior projection, and figure 3 is a right anterior-oblique view of the chest after the tap, showing the pneumopericardium, portions of the pericardium, and the cardiac outline. A tuberculin skin test (1/100 dilution) was negative.

It was decided that an opening of about 6 cm. in diameter be surgically constructed in the pericardium, communicating with the left pleural space. On March 29, 1947, under general oxygen-ether anesthesia with intubation, the chest was entered by resection of the costal cartilages of the third and fourth left ribs. The pericardium was tense and distended by a mixture of air and yellow serous fluid. It was thickened to approximately 3 to 4 mm. and of a grayish, glistening appearance with

a slightly granular internal surface. Finger exploration and investigation with a Cameron light failed to reveal the presence of a tumor or other disease entity. An opening of about 5 cm. in diameter was made between the pericardial and pleural cavities at a point low on the pericardium and at the same level in the lower portion of the pleura. A biopsy specimen was excised from the pericardium in the region of the incision. A catheter was inserted through the window into the pericardial sac and brought out through an incision at the costophrenic sulcus.

The patient had an uneventful postoperative course. Gradual absorption of the subcutaneous emphysema, pneumothorax, and hydropneumopericardium took place until x-rays on April 11 (the twenty-second postoperative day) revealed a normal cardiac size. Microscopic examination of the pericardial fluid was negative for malignant cells; the specimen of pericardium revealed slight thickening due to fibrosis,

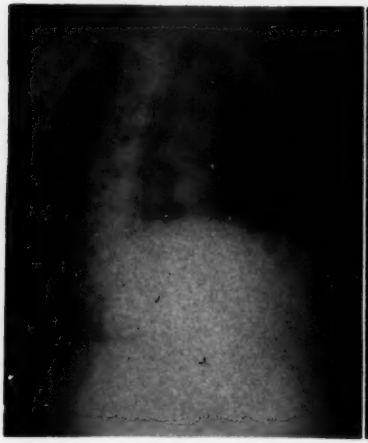

FIG. 3.

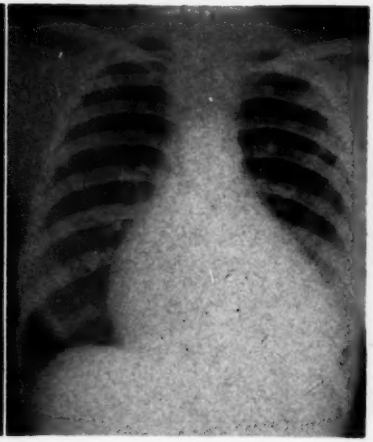

FIG. 4.

FIG. 3. Right anterior-oblique x-ray of chest after tap, showing pneumohydropericardium with fluid level.

FIG. 4. Postero-anterior x-ray of chest in 1949, two years following surgery, showing continued improvement in size of cardiac silhouette.

with round cell perivascular infiltration. The pathologic diagnosis was fibrosis of the pericardium.

Because of itching, thyroid extract was replaced, with benefit, by 6 mg. of thyroxin daily. The patient has remained free of all cardiac and respiratory difficulties, and has been an active housewife for a period of over six years. During this follow-up interval x-rays have revealed some enlargement of the cardiac silhouette, probably representing pericardial fluid. Figure 4 shows this enlargement of the heart shadow on x-ray of the chest. However, this has not progressed, and the heart size has not changed since 1949. The patient has had no digitalis or diuretics; her average basal metabolic rate has been minus 13%.

DISCUSSION

The pressing problem presented by this patient was the increasingly rapid re-accumulation of pericardial fluid resulting in cardiac tamponade. This could

not be controlled by mercurial diuretics and 360 mg. of thyroid extract per day. The serum cholesterol was not elevated, and the basal metabolic rate was frequently normal. It appeared doubtful that hypothyroidism alone could account for these observations. The microscopic findings of fibrosis of the pericardium suggested a low grade, chronic pericarditis as an etiologic process. However, it is possible that the pericardial thickening was the result rather than the cause of the long-standing presence of fluid in the pericardium. An effusion is more apt to occur with acute pericarditis, and it is not uncommon to find serosal thickening in other body cavities when they harbor fluid collections over long periods of time. Tuberculosis and neoplasm have been excluded. Another explanation for the pericardial effusion postulates the existence of an obstruction to the venous-lymphatic drainage of the pericardium. This might have resulted from a mediastinitis occurring postoperatively in association with the patient's thyroidectomy.

The left pleural space was uninvolved, as evidenced by the ability of the patient to collect free fluid in that area when in tamponade. The surface area of the pleura is relatively large and possesses drainage channels differing from those of the pericardium. When tamponade was relieved by a tap, pleural effusion fluid was readily absorbed. It was reasoned, therefore, that a foramen such as the one constructed would empty the pericardial fluid into the left pleural cavity, from which it would be easily absorbed. The surgical procedure has had no adverse effects and, although some pericardial fluid has re-accumulated, the patient has done well clinically. Absorption occurred from the left pleural surface, since no fluid has accumulated in that area. The partial re-accumulation of pericardial fluid, if this be the cause of the partially enlarged heart shadow, may be due to a closing down in the size of the "window." Studies with dyes or radiopaque material might clarify this point. Placing a catheter drain through the window is also a questionable technic. That stripping away a sizable area of pericardium may have significantly reduced the rate of formation of pericardial fluid also deserves consideration in evaluating the final result.

Summary

A patient with post-thyroidectomy hypothyroidism resistant to thyroid therapy developed recurrent pericardial effusion and cardiac tamponade. The pericardial effusion may have resulted from postoperative mediastinitis.

Cardiac tamponade and "congestive" heart failure have not recurred following the surgical construction of a foramen between the pericardial and pleural cavities. The patient has been followed for over six years postoperatively.

The rationale of a pleural-pericardial fenestration procedure is discussed. This new approach merits further study in relation to the management of chronic pericardial effusion and cardiac tamponade.

Acknowledgment

The author is indebted to Dr. Lew A. Hochberg for performing the fenestration operation on this patient.

PERIPHERAL NEURITIS AS A SEQUELA OF CARBON MONOXIDE ASPHYXIATION: A CASE REPORT*

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PERIPHERAL neuritis is an infrequent but well authenticated sequela of carbon monoxide asphyxiation. Since the number of cases on record is small, the following report is presented.

CASE REPORT

On Friday, December 7, 1951, while on a hunting trip in northern Michigan, a 50 year old male papermaker went to bed around 10:00 p.m. in his cabin. The stove, which used Pyrofax as fuel, was left burning. The patient recalls nothing further until the police arrived at 6:00 p.m. the following Monday night. He had told his wife he was returning home on Sunday, and when he failed to return the police were asked to investigate. When the cabin was entered by the police the stove was still burning. The patient was on the floor, doubled up. He could talk but is said to have been incoherent and delirious. He was unable to move his right arm, and both legs were very "hard" to the touch to a point above the midthigh. He could not stand, and could move his legs only slightly. The left arm appeared normal. His cabin mate had died approximately six hours before, according to the coroner's report. The patient was hospitalized for a week. He recalls little of the events of the first two days. Thereafter he was said to have been coherent and fully oriented. At the time of discharge he was able to walk with crutches. The upper extremities were said to be normal. For the next four weeks he spent much of his time in bed. He had lost about 18 pounds and was slowly regaining it. Six days prior to admission to the University Hospital, on January 21, 1952, he developed severe burning pain along the heel and outer edge of the right foot. This pain was continuous. There were occasional episodes of severe pruritus on the plantar surface of the right foot. There were frequent episodes of sharp, shooting pain in the medial and lateral aspects of the right leg. The left leg had had burning pain since he first regained consciousness, and shooting pains and itching had been present in the left lower extremity from the time of his recovery of consciousness. He complained of two areas of numbness, one just above the knee and another along the lateral aspect of the ankle and foot on the left. He stated that originally the areas had been larger than they were at present. Both legs were noted to swell when he was on his feet. The left arm had been perfectly all right until two weeks prior to his admission, at which time the fourth and fifth digits began to feel numb and there were some burning sensations in this area. He had no complaints referable to the right arm. Sleeping was difficult because of the pain. The patient noticed no deficiency in mental acuity or memory.

His past history revealed only sinus trouble and chronic "cholecystitis." The patient had smoked and drunk moderately and had used no habitual medications. There was no evidence of any familial diseases. The patient had no children.

Examination showed temperature, pulse and respirations to be normal. Blood pressure was 118/80 mm. of Hg. No abnormalities of the skin were noted. The head and neck were normal except for a defect resulting from sinus surgery in the

* Received for publication March 26, 1954.
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right frontal area. The lungs were clear to percussion and auscultation. His heart sounds were normal, with regular sinus rhythm and no murmurs. Examination of the abdomen showed some questionable right upper quadrant tenderness, and the liver edge was felt to be approximately 2 cm. below the right costal margin. A rectal examination was normal and the genitalia were normal.

A neurologic examination revealed an alert, oriented individual whose attitude was considered to be somewhat hostile. He performed all tests of calculation and memory very well. Examination of the cranial nerves was entirely within normal limits. Gait and station were normal. Tests of cerebellar function were well performed. Both deep muscle and superficial reflexes were intact and bilaterally equal throughout. There were no pathologic reflexes. A sensory examination disclosed an area of hypesthesia on the anterior aspect of the left leg corresponding to the distribution of the left lateral femoral cutaneous nerve. There were also hypesthesia, hypalgesia and impairment of other sensory modalities, with mild motor weakness in the distribution of the left ulnar nerve. There was sensory impairment of all modalities in the distribution of the area supplied by the trunk of the sciatic nerve. These changes went up to the midcalf region in the posterior lateral aspect of the left leg. No reflex change was noted, and no paresis of the left foot.

At the time of admission to the hospital the patient complained bitterly of pain of a burning nature around the plantar margin of both feet.

Laboratory investigation revealed a normal urinalysis. There were 15 gm. of hemoglobin, with 4,800,000 red blood cells. White blood count revealed a total of 10,900 white cells, with a normal differential. The blood Kahn was negative. X-ray of the chest was normal.

While in the hospital the patient was given intravenous Priscoline, which at first was thought to improve the burning paresthesia but later apparently exacerbated it. Protamide was also tried, without convincing benefits. He was given large doses of multivitamins, both orally and parenterally. After 12 days in the hospital there was mild improvement in the painful paresthesias but no real change in objective examination. He was discharged from the hospital on a high vitamin diet, supplemented by oral vitamin medications.

While in the hospital the patient appeared to be moderately depressed and somewhat hostile to the physicians and other personnel. There was no appreciable improvement in these affective symptoms up to the time of his discharge.

The patient was discharged February 13, 1952. He was seen again in July, 1952, at which time he had gained 30 pounds, and the burning sensation in both feet had completely disappeared. Examination at that time revealed minimal residual left ulnar paresthesia. Sensation had returned to the ulnar distribution, and motor strength was only very slightly if at all impaired. There continued to be some paresthesia and mild hypesthesia in a very small portion of the distribution of the left lateral femoral cutaneous nerve. At this time it was felt that the patellar reflex was slightly more active on the left. Examination of the previous areas of decreased sensation around the left ankle and foot showed a marked diminution in the extent of this area of sensory deficit.

The patient was again examined on October 6, 1952, 10 months after his accident. At this time he stated that he had noticed marked improvement in all symptoms. He felt that the onset of cold weather had caused some mild recurrence of sweating in his feet, and also noted that his feet were sweating more than they had before. He also complained of feeling generally tired and of fatiguing more easily. There was occasional cramping in both hands.

Examination revealed that only the tips of the fourth and fifth fingers were still dysesthesic. The area of the lateral femoral cutaneous nerve involvement on the left had narrowed to about the size of a silver dollar just above the knee. The area of involvement on the left leg was confined to a very small area around the lateral aspect

of the foot. He continued to have some unpleasant paresthesia in this area. Reflexes were symmetrical and equal, but were possibly slightly overactive in both lower extremities. Motor strength as tested by individual muscles was excellent, but when the patient's gait was tested it appeared that he had some difficulty walking on heels and toes.

He seemed much less depressed and certainly was more coöperative and less hostile than at the time of his original admission to the hospital.

Comment

Little has been written regarding peripheral neuritis resulting apparently from acute carbon monoxide poisoning. Meigs and Hughes [4] in their excellent article mention a pseudo recovery in approximately 10% of their patients. This was characterized as a mental relapse after a normal mental status. They stated that prolonged sensory changes were recorded only rarely. One patient did show evidence of radiculitis over the lower four cervical, last lumbar, and first sacral nerves. Sanger and Gilliland [5] and *Public Health Reports* [6] both mention evidence of a peripheral neuritis. The findings described were essentially the same as the authors', notably (1) burning sensation, (2) hypesthesia, (3) hypalgesia, (4) anesthesia, and (5) a shooting pain. Manifestations of central nervous system involvement were continued in the authors' patient, to symptoms of depression and hostility. The reported cases, as well as the authors', cleared with conservative treatment.

It is generally accepted that carbon monoxide poisoning causes demyelination and degeneration of the ganglion cells and globi pallidi, as well as hemorrhage and edema. Surprisingly little has been written giving a reason based on pathologic findings for peripheral neurologic symptoms. These symptoms cannot be overlooked, as they are part of the total picture of carbon monoxide poisoning and often last longer and are more annoying to the patient than the original acute symptoms.

Summary

1. Carbon monoxide inhalation is a common cause of poisoning.
2. Carbon monoxide as a cause of peripheral neuritis is rare.
3. A case of peripheral neuritis due to carbon monoxide poison is presented.

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CLINICOPATHOLOGICAL CONFERENCE *

Moderator: JOSEPH F. KUZMA, B.S., M.D., M.S., F.A.C.P., *Milwaukee, Wisconsin;* Participants: LOUIS R. LIMARZI, B.S., M.S., M.D., F.A.C.P., *Chicago, Illinois;* WESLEY W. SPINK, A.B., M.D., D.Sc. (Hon.), F.A.C.P., *Minneapolis, Minnesota;* WILLIS M. FOWLER, A.B., M.D., F.A.C.P., *Iowa City, Iowa;* and JOSEPH M. LUBITZ, A.B., M.D., F.A.C.P., *Wood, Wisconsin*

History:

Present Illness: The patient was a 64 year old Negro male porter admitted on May 9, 1951, with symptoms of arthralgia, chills, fever, pleurisy, and a cough which was productive of a rust colored sputum. His admission illness had begun with the symptoms of a common cold and within one week had progressed to a degree necessitating hospitalization with the abovementioned symptoms. Past history was noncontributory. Systemic review revealed that the patient had had occasional blood-streaked sputum for about one year, and that for the past six months he had had recurring epistaxis, lasting 10 to 15 minutes and occurring about once per month.

Physical Examination revealed a well developed, well nourished, Negro male whose temperature was 102° F. on admission. The following significant signs were noted: There was splinting of the right hemithorax, with a corresponding lag in the respiratory excursions. Coarse, moist râles were heard in the right base posteriorly, with dullness to percussion in the same area. Breath sounds were bronchovesicular in type. There was no change in tactile or vocal fremitus. Cardiovascular system was considered normal except for the admission blood pressure of 170/100 mm. of Hg. This was repeatedly normal, however, on further examinations. There was some spooning of the fingernails, together with a slight clubbing of the fingers.

Laboratory Work-up and X-ray Studies: On admission the red blood count was 2.4 million, with a hemoglobin of 9 gm. The white blood count was 3,000, with a slight shift to the left; otherwise a normal differential. The erythrocyte sedimentation rate was 125 mm. per hour Westergren. Urinalysis was within normal limits, and sputum culture revealed *Pseudomonas aeruginosa.* Repeat culture revealed a normal flora. Admission serology showed a negative Kahn with a 1-plus Wassermann, while both tests were called negative on several repeat examinations. Cold agglutinations were negative. PPD No. 1 was negative; PPD No. 2 was 1 plus. One blood culture was sterile. Three fungus cultures of the sputum were negative. Repeated electrocardiograms were within normal limits. During the patient's hospital stay, acid-fast cultures of four sputums, one bone marrow and one knee joint fluid were all negative. X-rays on admission confirmed the impression of pneumonia, right lower lobe.

Course in Hospital: Penicillin and supportive treatment for pneumonitis were initially instituted. On May 12 the penicillin was discontinued and Aureomycin was substituted. A fall in the temperature gradually followed, and on May 20 the patient was afebrile. On May 25 he developed a slight temperature elevation again, and from that date until shortly before his death he continued daily peak temperature elevations of 100° F. except for several scattered periods of from five to six days,

* Received for publication February 23, 1954.
From the Veterans Administration Hospital, Wood, Wisconsin.
Presented at Regional Meeting, Midwestern Section, American College of Physicians, Milwaukee, Wisconsin, November 21, 1953.

when he was completely afebrile. Bronchoscopy on May 15 revealed secondary endobronchial changes of the right bronchus. No specific endobronchial lesion was seen.

On May 16 the white blood count was 2,200, with 11 segmenters, 5 stabs, 7 juveniles, 1 myelocyte, 6 myeloblasts, 54 lymphocytes, 15 monocytes and 1 basophil. Five days later the white blood count was 1,400, with essentially the same differential. Sternal iliac marrow aspirations were "dry." Sternal marrow trephine was performed, and the slides were interpreted by two hematologists as subacute myelogenous leukemia, and by two others as possibly representing a maturation arrest with an agranulocytic peripheral picture.

On June 30 the patient was transferred to the Hematology Service, and at this time hepatomegaly was detected for the first time. A complete liver function study revealed a total cholesterol of 108 mg. %, A-G ratio of 1 : 1, zinc sulfate turbidity of 28.2 units, and thymol turbidity of 6.9 units as the only abnormal tests. Multiple transfusions were given during this entire hospitalization, but despite this his hemoglobin was never higher than 11.5 gm. and his red blood count never higher than 3.4 million, with a mean of 7 gm. hemoglobin and 2.2 million red blood cells. The white blood count fluctuated between 1,000 and 5,000, with a differential as previously stated. All antibiotics were used at one time or another and were all unsuccessful, except for one period of normal temperature lasting for one week following Terfonyl. This response could never be reduplicated with the same drug. On September 19 a hemarthrosis developed in both knees. Bleeding time was now 4 minutes 50 seconds; coagulation time, 2 minutes 45 seconds; no clot retraction occurred in 24 hours. Platelets were 70,000 and continued to remain as low or lower from this time on. Intermittent bleeding episodes next occurred from the nose, left ear and the gastrointestinal and genitourinary tracts. On October 17 his temperature was 101.4° F. and from then on remained elevated. Three walnut-sized, fluctuant tumor masses developed in the left axilla two weeks prior to his death. Nine days later these broke down and drained a greenish, foul-smelling, purulent material. Fever, malnutrition and lethargy gradually increased. The patient died on October 29 following a comatose state lasting for 12 hours.

Moderator: DR. JOSEPH F. KUZMA: You are now about to witness a completely spontaneous and unrehearsed panel discussion of the illness of an adult Negro male. The illness began as a respiratory ailment with pancytopenia. It ran a febrile fatal course in five and one-half months.

DR. LOUIS LIMARZI: Thank you for the introduction. The patient's present illness began with a "common cold," then followed by the classic acute bacterial, right lower lobe pneumonia. There is one question that arises at this point, namely, is this right lower lobe localization, which is a common one, on the basis of relative right lower lobe bronchus obstruction from "catarrhal" mucosal swelling following his "common cold"? Or does the partial bronchial obstruction represent a chronic disease, specifically bronchogenic carcinoma, or right lower lobe bronchiectasis? From both conditions one may have blood-streaked sputum for one year and the clubbing of fingers. The presence of *Ps. aeruginosa* would be in favor of chronic, stagnant infection of the lung. The bronchoscopic finding of secondary endobronchial changes could be found either in bronchiectasis or just above a bronchogenic carcinoma. We are not told whether the pulmonary lesion ever resolved, and furthermore, whether there were signs of heart disease.

The admission cardiac examination was normal, but nothing more is said about the heart. Why, then, the repeated electrocardiograms? The anemia and leukopenia cannot be explained on the basis of an uncomplicated bacterial pneumonia. Cases of low grade, subacute bacterial endocarditis have been reported in which fever and anemia have been the only manifestations of the disease. Could this be a rare case of subacute bacterial endocarditis from Pseudomonas? Seven cases of pyocyaneus subacute bacterial endocarditis have been reported. Five cases were associated with agranulocytosis and one case with thrombocytopenic purpura in a boy with disseminated lupus erythematosus. The original infection was right lower lobe involvement, and suppurative lymph nodes with greenish foul pus from the left axilla are suggestive of Pseudomonas. Brucellosis is to be considered, especially because Dr. Spink is a discussant. Brucellosis can be associated with a bronchial type of pneumonia as well as a granulomatous hepatitis and leukopenia with moderate anemia. However, to have the severe marrow depression and peripheral blood abnormality would again suggest the presence of an endocarditis to explain so overwhelming a picture. The granulomatous lesion seen in the bone marrow in some cases of acute brucellosis, originally described by Dr. Spink and Dr. Sundberg, was not mentioned in the histologic description of the bone marrow. In an attempt to arrive at a diagnosis, the blood findings must be considered in relation to a leukemic process or a leukemoid reaction. The anemia, leukopenia, thrombocytopenia and the left shift in the granulocytic elements with increased number of myeloblasts speak for a leukemic process. There is some indication of a *hiatus leukemicus,* but this is overshadowed by the low total white count. There is no mention as to the morphologic characteristics of the myeloblasts and platelets. Abnormalities of these cellular elements would favor a leukemic process. The lack of any nucleated red cells in the blood also favors leukemia rather than a leukemoid blood reaction. Sternal and iliac crest marrow aspirations were "dry," and it was necessary to perform a marrow trephine. A "dry lap" is seen in a number of blood dyscrasias, one of which is leukemia. The histologic examination of the marrow was interpreted as a granulocytic leukemia and maturation arrest with an agranulocytic peripheral blood picture. Marrow smears apparently were not obtained. Description of the marrow findings, which would aid in the diagnosis, is not mentioned. It would be of interest to know the level of maturation arrest, that is, whether it was myeloblastic, progranulocytic or myelocytic. Arrest at the myeloblastic level would speak for a leukemia. If a plasma cell reaction were present, this would aid in the differentiation of a leukemic and infectious process. An infection is commonly associated with leukemia, and inasmuch as pyocyaneus is of low virulence, and has come more into prominence since its antagonists have been killed off by sulfa, penicillin and streptomycin, it is more common in debilitated persons. If we try to maintain a unity of diagnosis, I must

conclude that the patient had a subacute granulocytic leukemia and a metastatic carcinoma of the lung.

DR. WESLEY SPINK: You'll gather from my remarks that this is totally unrehearsed, because I am going to take an entirely different line of reasoning. As a matter of fact, whenever I approach a clinical-pathological conference or listen to one, I am not concerned too much with the final diagnosis, but I'm awfully concerned with a man's reasoning, that is, how he arrived there. As I read this protocol over, the outstanding feature to me was that we have a 60 year old Negro who had been coughing up blood-streaked sputum for a year. When we have a Negro who has been coughing up blood, we must think of tuberculosis first, malignancy second, and bronchiectasis third. Then we have an abrupt change in his course just before he came into the hospital. This still could represent an infectious process which extended over a period of several months, or an abrupt change in the course of a malignancy with a secondary infection. The outstanding features again when he came in were, as Dr. Limarzi has said, pneumonia with consolidation at the base of the right lung. Maybe he had atelectasis. No x-rays are available. From a laboratory point of view, the outstanding features are a severe anemia with leukopenia and an accelerated sedimentation rate. I'd place considerable stress upon a sedimentation rate of 125 mm. done with the Westergren technic; and even in spite of the anemia, I think that this is very significant. Features that disturb me are negative acid-fast cultures of the knee joint fluid, sputum and bone marrow. However, I might say that in fever of unknown etiology extending over a period of several months, a recent survey of our experience at the University Hospital over a period of 15 years has revealed that the most treacherous disease of an infectious origin has been tuberculosis. It has been missed time and time again. It's still a most treacherous disease of a chronic nature that confronts us, so I'm not going to be deterred too much by a negative bacteriologic finding because I've seen that occur. We note that the only positive bacteriologic findings are *Ps. aeruginosa* in the sputum. That's a very common finding today. I'm not so sure that it has any significance. In a debilitated, sick individual one will find these organisms without a primary infectious disease's being present. I can hardly believe that this man's death is due to Pseudomonas. I just can't make a diagnosis of bacterial endocarditis of a chronic nature without the presence of a murmur, though it does occur. I've never encountered it. It is extremely rare in our experience. Acute bacterial endocarditis is another matter. This may occur without murmurs being heard. He was given Aureomycin, with some improvement. Then we have a progressive depression of the bone marrow, with severe anemia, bleeding, leukopenia, thrombocytopenia and, finally, fluctuant tumor masses present in the axillary region, and death. It seems to me that there are three possibilities: First, can this be a primary blood dyscrasia as Dr. Limarzi has pointed out; that is, leukemia with depression of the bone marrow and secondary infection? I think the hepatomegaly can go with a chronic

nutritional deficiency and fatty infiltration of the liver. This case could represent a primary blood dyscrasia with a secondary fungus infection. We have seen this sequence of events with cryptococcosis and blastomycosis, and I have seen systemic sporotrichosis do this. Could this be a primary infection with a secondary depression of the bone marrow? There is nothing inconsistent with the story for disseminated tuberculosis, or sporotrichosis, cryptococcosis, actinomycosis or blastomycosis. Finally, could *Ps. aeruginosa* be the cause of death? I would rather doubt it without other localizing findings, and I find no evidence of such localizing findings. It's a very difficult thing to come to a conclusion. A precise diagnosis has been asked for. I shall have to conclude—and I don't know that the pathologist can prove it one way or the other—that the man had disseminated tuberculosis with associated bone marrow depression involving all of the elements of the bone marrow. It was not brucellosis!

DR. KUZMA: Thank you, Dr. Spink. Dr. Fowler.

DR. WILLIS FOWLER: I don't feel that I have much to contribute to this discussion because I find that our lines of thinking go along similar channels. I would feel from the manifestations that are presented that there was a good possibility that this individual had bronchiectasis. The history of blood-streaked sputum for the period of a year, clubbing of the fingers, and other evidences of a chronic infection are suggestive, so that I was inclined to think of bronchiectasis with a pneumonitis around the bronchiectatic areas. Second thought in my mind was along Dr. Spink's line of thinking, the possibility of tuberculosis. That certainly must be considered in this individual with a generalized spread involving the marrow, liver and spleen. However, my first thought, as I said, was bronchiectasis. That brings up the question which Dr. Limarzi raised as to whether this was a subacute myeloid leukemia accounting for the blood picture which he had. Admittedly, that can occur with a tuberculous infection, and that is a definite possibility. But reasoning along those lines, I was more inclined to think that probably it was a primary blood dyscrasia, a chronic myeloid leukemia. The principal objection to that as far as I can see is that it is a little too simple, and consequently I'm very suspicious that the case presented was not quite so clear-cut as one might think. However, I would follow along those lines, and without repeating the evidence any more, feel that a bronchiectasis with a chronic myeloid leukemia would certainly explain all of these manifestations.

DR. KUZMA: Thank you, Dr. Fowler. Dr. Lubitz.

DR. JOSEPH LUBITZ: The external examination presented an emaciated Negro. There were purpuric spots over the entire body, over the shoulders, the arms, the abdominal wall, also in the conjunctivae and within the mouth. These ranged from a few millimeters to 2 cm. in size. The lymph nodes in the left axilla were found as described in the protocol. These were soft, fluctuant masses, draining from three sinuses. The right epitrochlear lymph node was also enlarged to 1 cm. On the dorsum of the body there was a

sacral decubitus ulcer. On internal examination, purpura was also present on the serosal surfaces of the pleura, the epicardium and the peritoneum, and also in the gastrointestinal tract and in the left renal pelvis. In the chest there was one calcified tracheobronchial lymph node, measuring 2.5 cm., indicating old tuberculosis. The pleura of the right lung was adherent at the costophrenic angle. The left pleural space was entirely obliterated by old adhesions. The lungs showed moderate edema, and there was hypostasis. Small foci of fibrosis were found. The pneumonia or pneu-

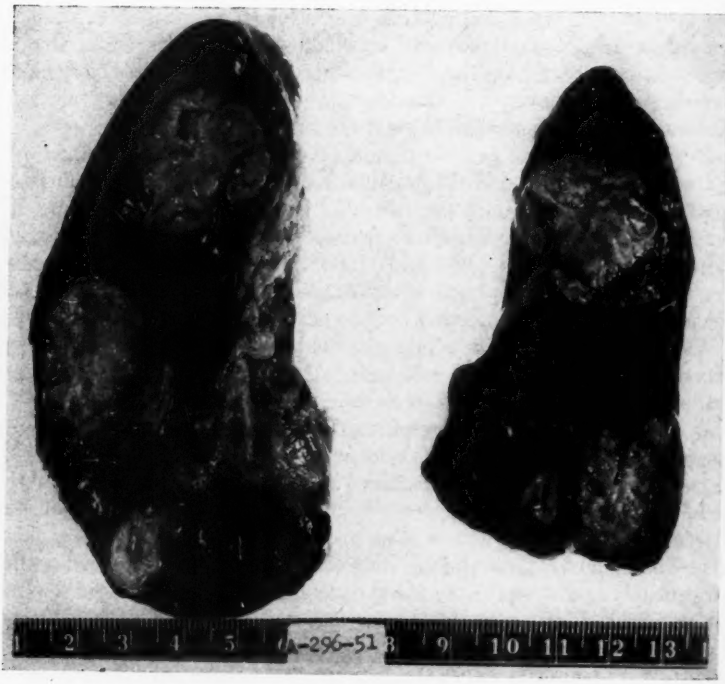

FIG. 1. Spleen, gross. Multiple caseous tuberculous abscesses.

monic process which was described five months before death on x-ray and physical examination was no longer present. The heart was not particularly altered; it weighed 325 gm. The right ventricle measured 2 mm. in thickness. The wall of the left ventricle was somewhat hypertrophied, measuring 16 mm. The myocardium was pale, a tan-red in color, and soft, indicating general toxic damage to the organs. The coronary vessels showed moderate arteriosclerosis. The liver was slightly enlarged, weighed 1,960 gm., and was flabby and brownish red in color. Several nodules were seen, on both the external and the cut surface, ranging in size from 1 mm. up to about

1 cm. Some of these were soft, and a greenish yellow material could be expressed. The spleen was slightly enlarged, weighing 240 gm. (figure 1). There were two splenic abscesses, one measuring 4 cm. and the other 3 cm., which bulged above the surface and which contained a thick, creamy green material. Smaller nodules were also present on cut surface. The adrenals showed nothing unusual. The kidneys were of usual size; they were flabby and finely granular, and showed small subcapsular hemorrhages. In the left kidney there was a nodule measuring 3 mm. which was also soft. In the gastrointestinal tract the stomach showed atrophy and, as I have already indicated, small hemorrhages throughout the intestinal tract. This is a photomicrograph of the peripheral smear taken during life. The man had a leukopenia, and it was therefore difficult to get more white cells in one field. Here is a myeloblast, and this is a myelocyte. This is the trephine bone marrow section taken before death, and at autopsy the bone marrow showed the same picture. It is a moderately full bone marrow (figure 2). Nevertheless, it is not quite so crowded as one sees in classic acute leukemia. The presence of fat spaces indicates that we do not have a full leukemic bone marrow. Even at this low power magnification all of the bone marrow elements are present—megakaryocytes, red cells, white cells—without predominance of any one cell type. Higher power shows increase of granulocytic cells, but they are not 'blasts. Mature granulocytes are also considerably decreased. At this point one cannot make any definite diagnosis. One can suggest chronic myelogenous leukemia or maturation arrest of the myeloid series, which doesn't say very much.

The liver and spleen, kidney and lymph nodes microscopically showed caseous tuberculosis with large numbers of tubercle bacilli. It's a soft lesion with very little tissue reaction in the way of giant cells, fibrosis or lymphocytes. The autopsy examination reveals, therefore, disseminated tuberculosis. However, the clinical course was one which would be considered leukemia. Now in developing the case, we must go back to history. There have been repeated attempts to associate tuberculosis with leukemia. In 1883 and in subsequent writings Landouzy[1] described a disease which he called typhobacillosis. Unlike miliary tuberculosis, it was a typhoid-like state with fever, enlarged spleen and liver, leukopenia, lymphocytosis, and a septic clinical picture. Autopsy studies later showed it to be an unusual form of tuberculosis in which degenerative changes rather than the typical tuberculous tissue reaction were found. Areas of necrosis were described in which the tissues were filled with tubercle bacilli. Subsequently, similar cases with a leukemic blood picture were described in the German and American literature.[2, 3, 4] Although in most instances the hematologic picture showed features of myelogenous leukemia, in a few instances lymphocytes and monocytes were prominent. There are two possibilities to relate tuberculosis with the leukemic picture. The first is that we are dealing with an underlying leukemia which, because of lowered resistance, permits tuberculosis to develop. The second is that the leukemoid reaction is due

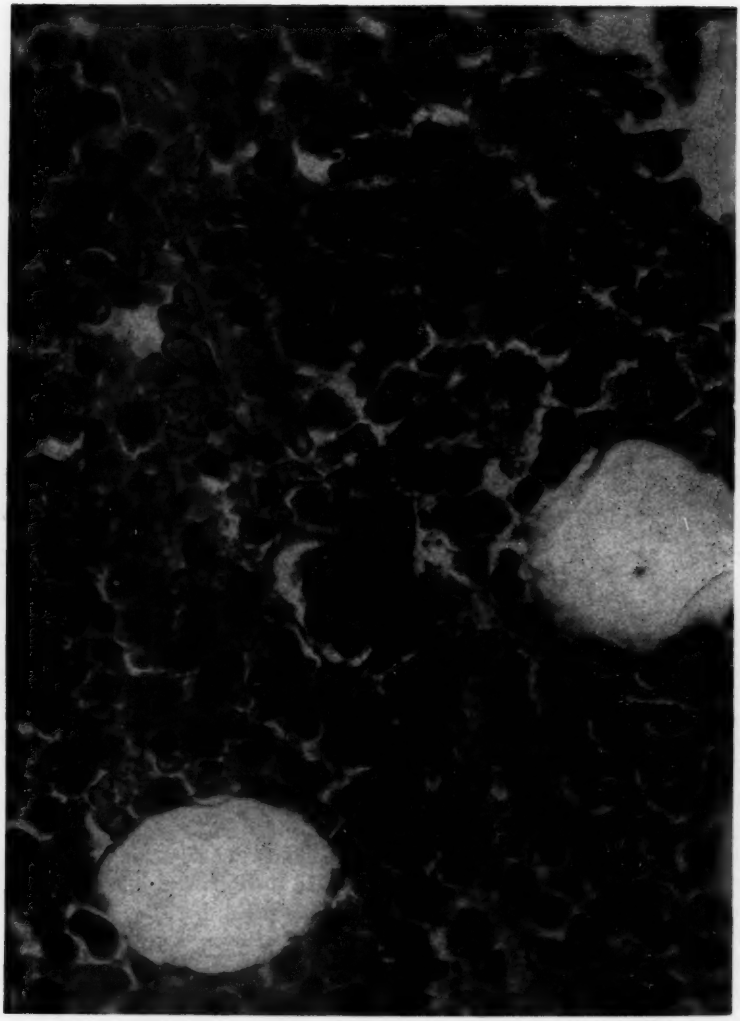

FIG. 2. Photomicrograph of bone marrow biopsy (325 ×). The marrow is moderately active. All elements are present. Mature granulocytes are decreased.

to the tuberculosis. In substantiation of the second hypothesis, one can cite animal experiments by Yersin[5] in which tubercle bacillus cultures were injected into rabbits with development of an essentially similar picture. Pathologic findings are not the same in all cases. In some instances there is practically no leukemic tissue infiltration as in this case. In others, the bone marrow shows only leukemic infiltration. In a few, one finds a more fully developed leukemic picture similar to that found in the classic leukemia. It is of interest that this patient had 15% monocytes, and perhaps that may have been a clue to tuberculosis. I don't think there is any answer at this point as to what this peculiar disease actually is. Perhaps the only way that this could be solved would be to take a case that has a leukemic blood picture and clinical findings of leukemia, give the patient anti-tuberculosis treatment, such as streptomycin, and if the leukemia disappears, then I think we would be justified in saying that we were dealing with tuberculosis. In summation, the case leaves the question with us, What is leukemia?

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ERRATUM

February, 1955, page 332, in the last sentence of the third paragraph, the word "decreased" should be changed to read "increased."

EDITORIAL

RESISTANCE OF MICROCOCCI (STAPHYLOCOCCI) TO ANTIBIOTICS

TREATMENT of severe staphylococcal infections has always presented difficult problems which have by no means been eliminated by the advent of antibacterial drugs. The sulfonamides furnished relatively little help, although sulfathiazole for a time proved effective in many cases of staphylococcal infection of the urinary passages and occasionally in generalized infections.

The advent of penicillin, however, apparently opened up a new era when it was found that these organisms were almost uniformly sensitive to penicillin and that the drug was highly effective clinically. The immediate result, when adequate quantities of penicillin were available, was a marked reduction in mortality and a shortening of the period of illness. Thus Spink [1] reported that the mortality in cases of staphylococcal septicemia fell during 1942 to 1944 from over 80 per cent to 29 per cent in the University of Minnesota Clinics. As the use of penicillin became more extensive in the community, however, strains of staphylococci highly resistant to it were isolated with increasing frequency until by 1951, 50 per cent of the strains from hospital patients were resistant.[2] With this there was a resurgence in the mortality rate which by 1953 reached about 50 per cent in cases of generalized infection.[1] Resistance to streptomycin also was usually acquired with great promptness, but at first most strains of staphylococci, regardless of their behavior to penicillin, were sensitive to the newer so-called "broad spectrum" antibiotics. Since staphylococci are now rapidly developing resistance to these newer drugs as well, the problem becomes of great importance both from the academic and the practical standpoints.

There are two types of resistance to penicillin which staphylococci may acquire.[3] If a sensitive strain is grown in media containing small but increasing concentrations of penicillin, a substantial degree of resistance may gradually be built up. Such cultures may show morphological changes, particularly growth in minute "G colonies." They also show biochemical alterations, and penicillin-dependent strains have been obtained, but they do not form penicillinase. This type of resistance probably may develop in vivo since G colonies may appear in cultures from closed lesions of treated patients. This change is only temporary, however, the original sensitiveness returning as soon as the penicillin is removed, and it is of relatively little practical importance.

[1] Spink, W. W.: Staphylococcal infections and the problem of antibiotic-resistant staphylococci, Arch. Int. Med. **94**: 167–196, 1954.

[2] Spink, W. W.: Clinical and biological significance of penicillin-resistant staphylococci, including observations with streptomycin, Aureomycin, chloramphenicol and Terramycin, J. Lab. and Clin. Med. **37**: 278–293, 1951.

[3] Prissick, F. H.: Antibiotic-resistant staphylococci and related infections, Am.. J. M. Sc. **225**: 299–319, 1953. (Good general review.)

The second type appears abruptly and is usually marked in degree or rapidly becomes so, and it is permanent, being transmitted indefinitely in vivo or in vitro like a genetically determined character. Such resistant strains have acquired the power to form penicillinase, a ferment that specifically inhibits or destroys penicillin. They differ in no other demonstrable way from the sensitive strains, either in morphology, biochemical characters, pathogenicity or virulence. It is generally believed that such strains arise as a mutation, either spontaneously or possibly under the influence of penicillin. That such mutations occur spontaneously is shown by the isolation of a few resistant strains before penicillin came into use.[4] That such strains may emerge while patients are under treatment is indicated by the isolation by blood cultures from patients with staphylococcal septicemia of strains which early in the disease were sensitive but later became highly resistant.[5] Many similar observations have been made in cases with open lesions, but in them the possibility of cross infection from other sources can not be entirely excluded. The part, if any, that penicillin plays in instigating the mutation is debatable, but there is no question that its major rôle is in selectively determining the survival of a few resistant mutants at the expense of the overwhelming majority of sensitive organisms.

A similar selective elimination of sensitive strains may be brought about in symptomless carriers of pathogenic staphylococci to whom the antibiotic is administered for some unrelated infection. This may permit the overgrowth of resistant survivors or by altering the normal flora facilitate the implantation of resistant strains from outside sources.

Staphylococci are abundant on the human body and in its environment—on the skin, in the nose, pharynx and intestinal tract. Many strains are doubtless harmless, and recognition of pathogenic strains is not always easy. Most pathogens are hemolytic pigment formers, but the most dependable practicable test at present is the capacity to form coagulase, a ferment that coagulates normal plasma. All staphylococci, including those forming coagulase, resist desiccation and survive in dust, on clothing, in the bed clothes. They are readily disseminated through the air or on the hands, contaminating open lesions or establishing themselves as saprophytes in normal subjects.

Staphylococci have not been satisfactorily subdivided into types. Many of them, however, have been assigned to less sharply defined groups on the basis of their susceptibility to various species of bacteriophage. On this basis it is often possible to show that a resistant strain can be, or can not be derived from a sensitive strain which it has replaced. It has also been found that mutations are not evenly distributed in the different groups, but in a given locality most resistant strains fall into one group (Group 3,

[4] Knight, V., and Holzer, A. R.: Quoted by Spink,[1] p. 181.
[5] Hirsh, H. L., et al.: Organisms resistant to penicillin obtained from patients, Arch. Int. Med. 82: 310–318, 1948.

in Bellevue Hospital, N. Y., e.g.).[6] In other localities, most resistant strains may fall into a different group, and this may change from year to year.[7] Such observations suggest that mutations need not occur very frequently, but that once a resistant strain has appeared and established itself, cross infection from subject to subject is a far greater immediate source of danger than the repeated occurrence of fresh mutations.

This view is supported by the rapidity with which new born infants in a hospital nursery become infected. Thus, in an Australian hospital[8] 90 per cent of the infants became nasal carriers within a week. Similar observations have been made in British hospitals[9] and in this country, with from 50 per cent to 90 per cent of the strains resistant to penicillin. The strains found corresponded to those cultivated from the dust or from the nares of the nurses rather than from the mothers.

That the increasing proportion of resistant strains is directly correlated with the duration and extent of the use of antibiotics is clear from numerous reports from various parts of the world. Thus Barber[10] found that the percentage of resistant strains isolated from patients rose from 14 per cent in 1945–1946 to 38 per cent within one year and to 59 per cent in 1948. Similar figures have been reported by Rountree[7] and by various observers in this country (reviewed by Spink[1]). Dowling et al.[11] studied a group of 54 hospital patients and 209 contacts. Of the former, 74 per cent yielded a positive culture on discharge, of which 69 per cent were resistant to penicillin. Four to six weeks after returning home, however, the figure had fallen to about 35 per cent, of which 30 per cent were resistant. Of the contacts, an average of about 33 per cent yielded staphylococci, 25 per cent being resistant, and there was little change in these figures during the period of observation.

That the number of carriers of resistant strains tends to reach an equilibrium is also suggested by the observations of Altemeier,[12] who observed a fall in sensitive strains from 96 per cent in 1942 to about 54 per cent 10 years later, but with no significant variation during the past three years.

As the number of staphylococcal infections resistant to penicillin increased, one turned naturally to the newer antibiotics, the tetracyclines (Aureomycin and Terramycin). At first a large majority of the micro-

[6] Knight, V., and Holzer, A. R.: Studies on staphylococci from hospital patients. I. Predominance of strains of Group III phage patterns which are resistant to multiple antibiotics, J. Clin. Investigation 33: 1190–1198, 1954.

[7] Rountree, P. M., and Thomson, E. F.: Incidence of antibiotic-resistant staphylococci in a hospital, Lancet 2: 262–265, 1952.

[8] Rountree, P. M., and Barbour, R. H. G.: *Staphylococcus pyogenes* in new-born babies in a maternity hospital, M. J. Australia 1: 525, 1950.

[9] Martyn, G.: Staphylococci in the new-born, Brit. M. J. 1: 710, 1949.

[10] Barber, M., et al.: Infection by penicillin-resistant staphylococci, Lancet 2: 641, 1948.

[11] Dowling, H. F., Lepper, M. H., and Jackson, G. G.: Observations on the epidemiological spread of antibiotic-resistant staphylococci with measurements of the changes in sensitivity to penicillin and Aureomycin, Am. J. Pub. Health 43: 860–868, 1953.

[12] Altemeier, W. A., et al.: Critical re-evaluation of antibiotic therapy in surgery, J. A. M. A. 157: 305–309, 1955.

coccal strains (but not quite all) were highly susceptible to them. With increasing use, however, resistant strains speedily appeared, even more promptly than with penicillin. This was probably due in part to their widespread use in the community for all sorts of undiagnosed fevers because of their "broad spectrum" and supposed effectiveness in "virus infections." By February, 1952, Finland et al.[13] found about 30 per cent of the strains resistant, and the number is increasing. For example, Knight and Holzer [6] studied a series of cultures from patients at Bellevue Hospital which on admission were largely susceptible to the tetracyclines. "Within a short time," however, they were replaced in two-thirds of the subjects by resistant strains (also resistant to penicillin). Unfortunately resistance to one tetracycline usually means resistance to all of them. The story of penicillin has virtually been repeated.

A troublesome complication following the use (most often) of the tetracyclines for infections of any sort is the development of an active infection by resistant strains of staphylococci previously latent, incited apparently by the disturbance in the bacterial flora which follows elimination of those species sensitive to the antibiotic. This was pointed out prominently by Jackson, Finland et al.,[14] who emphasized the frequency with which serious or fatal staphylococcal infection of the lung followed elimination of a pneumococcal lobar pneumonia, by Terramycin. He also reported cultivating staphylococci from the stools and sputum of 12 of 18 patients with severe diarrhea, of which all but one tested were resistant to Terramycin. Many similar cases have since been reported, quite frequently surgical patients after abdominal operations, most often after oral administration of a tetracycline, less often after other antibiotics. The symptoms are attributed to a toxin, "enterotoxin," elaborated by the staphylococci and believed to be identical with that concerned in cases of staphylococcal food poisoning. If not recognized and properly managed it may proceed to an extensive diphtheritic enterocolitis with dehydration, profound shock and a speedily fatal termination.[15] The organisms are usually present in enormous numbers in relatively pure culture, easily demonstrable on suitable media but not on media favoring Salmonella or Shigella.

Dearing et al.[16] reported a series of 44 such cases, 40 of whom had received one or both tetracyclines, with 41 positives cultures, 38 of which were resistant to Aureomycin, Terramycin and streptomycin. As cases clinically and pathologically similar were observed as rarities in pre-antibiotic days

[13] Finland, M., and Haight, T. H.: Antibiotic resistance of pathogenic staphylococci. Study of five hundred strains isolated at Boston City Hospital from October 1951 to February 1952, Arch. Int. Med. **91**: 143–158, 1953.

[14] Jackson, G. G., et al.: Terramycin therapy of pneumonia; clinical and bacteriological studies in 91 cases, Ann. Int. Med. **35**: 1175–1202, 1951.

[15] Speare, G. S.: Staphylococcus pseudomembranous enterocolitis, a complication of antibiotic therapy, Am. J. Surg. **88**: 523–534, 1954.

[16] Dearing, W. H., and Heilman, F. R.: Micrococcic (staphylococcic) enteritis as a complication of antibiotic therapy, Proc. Staff Meet., Mayo Clin. **28**: 121, 1952.

("postoperative pseudomembranous enterocolitis"), these authors question the invariable association of staphylococci with this syndrome. Failure to demonstrate staphylococci in the earlier cases, however, may well have been due to use of unsuitable cultural methods.

The observations of Dearing were made when erythromycin was first coming into use. These strains were nearly all susceptible to it, and the substitution of erythromycin for the tetracyclines usually resulted in prompt cure. The early reports of its use in ordinary staphylococcal infections were favorable.[17]

Erythromycin, however, promises to offer only a temporary respite from the inadequacies of the older drugs. Abundant evidence is accumulating that resistant strains of staphylococci may emerge during treatment with it. In one case reported a typical attack of enterocolitis ensued when resistance to the drug developed during treatment with it. Strains resistant to erythromycin have appeared during treatment in several other cases. The observations of Dowling et al.[18] are especially significant. In September, 1952, strains of staphylococci isolated from patients and hospital personnel were all sensitive. When extensive use of the drug in the hospital was begun, resistant strains appeared, and after four months about 60 per cent of the strains were resistant, both those from hospital personnel and from patients on discharge. After use of the drug was largely discontinued, the percentage of resistant strains fell progressively to about 20 per cent after 17 months. While the drug was in use, resistant strains appeared in about 5 to 10 per cent of entering patients, but these largely disappeared after use was stopped.

Resistance to antibiotics acquired by certain strains of many microorganisms is a familiar phenomenon, but of them all, the staphylococci have proved the most recalcitrant and troublesome. The increasing frequency of strains resistant to all the currently available "safe" antibiotics is highly disturbing,[3] and the prospects of finding a new antibiotic to which staphylococci will not become resistant seem bleak. The problem is rather how best to use the means available and conserve their effectiveness. The most fundamental but most difficult measure would be curbing the indiscriminate dispensing of antibiotics in the community for undiagnosed infections, ordinary "colds" and other minor illnesses. This has now been shown to be not only useless and wasteful but in varying degree dangerous and a positive disservice to the patient and to the community at large. The risk of establishing a resistant strain of organisms, of disturbing the normal flora and inciting and substituting a serious "untreatable" infection for some relatively harmless one seems definitely to outweigh any benefit that may be anticipated from their use as a routine prophylactic measure. Even the advisability

[17] Herrell, W. E., and Martin, W. J.: Erythromycin for infections due to *Micrococcus pyogenes*, J. A. M. A. **152**: 1601, 1953.

[18] Dowling, H. F., Lepper, M. H., and Jackson, G. G.: Clinical significance of antibiotic-resistant bacteria, J. A. M. A. **157**: 327–331, 1955.

of the routine administration of antibiotics preoperatively should be reassessed, particularly the oral administration of tetracyclines, especially if the subject is a carrier of a resistant strain of staphylococcus in the pharynx or intestine.

The staphylococcus is becoming a serious problem in surgical wards.[19] In some hospitals postoperative wound infections and superinfection of burns and other superficial lesions with strains of staphylococci resistant to antibiotics has been disturbingly frequent. The situation is reminiscent of that created by the streptococcus in the maternity wards a century ago. Rigid asepsis is needed in the wards as well as in the operating room, and perhaps less dependence upon antibiotics to compensate for slips in technic, but the problem of viable organisms in the dust and bedding is really difficult.

These observations emphasize the importance of preliminary cultures and tests of sensitivity which should be repeated later as a guide if treatment is not adequately effective. In severe infections, pending such information, treatment may have to be started blindly, with those antibiotics found most frequently effective toward staphylococci at the time; at present most often erythromycin, perhaps combined with chloramphenicol or even bacitracin [1] if renal function is adequate. Relatively few strains have been found resistant to the latter two drugs, doubtless because fear of toxic effects has largely prevented their indiscriminate use.

The simultaneous administration of two antibiotics has theoretical advantages in that mutants resistant to one are not likely to have become simultaneously resistant to the other. The fear that one antibiotic may antagonize another, based on laboratory studies, has not thus far been borne out by clinical observations.

If a drug is given, treatment should be intensive, the dose should be ample, and it should be continued until the maximum effect has been obtained unless resistance to it appears during treatment. General supporting measures should be utilized fully, and surgical drainage carried out when indicated as promptly and vigorously as in pre-antibiotic days. Pathogenic strains of staphylococci resistant to the antibiotics are now even more dangerous than hemolytic streptococci. Patients harboring them should be effectively isolated. If asepsis in hospital wards is adequate to prevent cross infection, if antibiotics are withheld when not indicated, and if adequate care is exercised in their selection and administration most of the progress that has been achieved in the treatment of these infections may still be maintained.

PAUL W. CLOUGH

[19] Howe, G. W.: Postoperative wound infections due to *Staphylococcus aureus*, New England J. Med. **251**: 411–417, 1954.

REVIEWS

The Pineal Gland: A Review of the Physiologic Literature. By JULIAN I. KITAY and MARK D. ALTSCHULE. 280 pages; 14.5 × 22 cm. Published for the Commonwealth Fund by Harvard University Press, Cambridge. 1954. Price, $5.00.

Endocrinologists will be grateful for this critical evaluation of the literature on the pineal gland, published for the Commonwealth Fund by the Harvard University Press. Over 1700 papers are listed in the bibliography, including those written in the Japanese as well as in the Slavic tongues. The sheer bulk of this scientific writing appals one, particularly as it adds up to so very little. The authors are to be congratulated on undertaking the Herculean task of selecting those papers worthy of serious comment. Their chief criterion for inclusion was the statistical significance of the data presented. As a result their final conclusion that "Although the available physiologic and clinical data justify the presumption that the gland is functional, its functions cannot yet be defined," carries the ring of conviction.

In spite of this cautious statement, it is obvious from the content of the book that the authors feel that if the pineal gland does anything it somehow modifies gonadal function. There is strong suggestive evidence that in the absence of the pineal gland the gonads are bigger, the gonadotrophic content of the pituitary is higher, the estrus cycles are longer, and the vaginae of rats open sooner. Clinical evidence derived from the study of pineal tumors also supports this view. Unfortunately, studies on the effect of the injection of pineal extracts are for the most part inconclusive, although some experimental work, done by the authors themselves, bears out the conclusions derived from a study of the effects of pinealectomy. There is also good evidence that the pineal gland somehow participates in the control of the pigmentary effector system of the lower vertebrates.

Since the book is limited strictly to a consideration of the possible endocrine function of the pineal body, there is no review of the literature dealing with its rôle as a photoreceptor.

It is hoped that the publication of this book will stimulate further interest in the pineal gland and that future investigators will heed the authors' admonition to perform their experiments on a sufficiently large group of animals to permit statistical analysis of the results.

DIETRICH C. SMITH

The Clinical Examination of the Nervous System. 10th Ed. By G. H. MONRAD-KROHN, M.D., F.R.C.P., Professor of Medicine in the University of Oslo. 428 pages; 14.5 × 22 cm. Paul B. Hoeber, Inc., Medical Book Department of Harper & Brothers, New York. 1955. Price, $7.50.

This is the tenth edition of an invaluable book by Dr. Monrad-Krohn. Basically, the book remains the same as the previous editions presenting the methods used in examination of neurologic patients in the author's clinic. The chief change is the increase in the number of illustrations and drawings. As accessory methods of examination have become more useful it has been necessary for the author to expand his sections on electroencephalography, electromyography, pneumoencephalography and angiography. The emphasis is still placed, however, on clinical observation and examination of the patient, rather than the use of the accessory methods. Although there is no bibliography, as such, there are numerous references in the form of foot notes directing the interested student to the appropriate collateral reading. The page size and the print are larger than in previous editions, with somewhat fewer pages. This improves the ease of reading but takes the volume out of the classification of a handbook.

The Clinical Examination of the Nervous System was planned for students and will be most useful to them and to their teachers. The tenth edition has preserved the excellence which has typified the previous editions.

CHARLES VAN BUSKIRK, M.D.

The Digestive Tract in Roentgenology. 2nd Ed. By JACOB BUCKSTEIN, M.D., Assistant Professor of Clinical Medicine, Cornell University Medical College; Visiting Roentgenologist (Alimentary Tract Division), Bellevue Hospital, New York City; Attending Gastroenterologist, Beth David Hospital, New York City; Consultant to Central Islip State Hospital, New York; Norwalk General Hospital, Norwalk, Connecticut; Good Samaritan Hospital, Suffern, New York; Formerly Consultant in Gastro-enterology to the U. S. Public Health Service and the U. S. Veterans Bureau. Two volumes; 1202 pages; 18 × 26 cm. J. B. Lippincott Co., Philadelphia. 1953. Price, $30.00.

The second edition of *The Digestive Tract in Roentgenology* is written in two volumes. Volume one includes diseases of the hypopharynx, esophagus, stomach and duodenum whereas lesions of the remainder of the gastrointestinal tract and its related organs are discussed in volume two.

The author has organized a large amount of material very well and placed emphasis upon those lesions most commonly encountered by the radiologists, gastroenterologists and the internists. In each entity the roentgenologic features are stressed and well illustrated, though there is good correlation between clinical, roentgenologic and pathologic aspects. Frequent case histories are presented to stress and correlate those outstanding clinical, roentgenologic and pathologic points.

The book is easy to read and will provide a very useful reference for all those medical specialists interested in the gastrointestinal tract.

J. M. D.

Die Angiographie zur Erkennung, Behandlung und Begutachtung peripherer Durchblutungsstörungen. By Dr. Med. Habil. H. W. PÄSSLER. 115 pages; 21 × 30.5 cm. (paper-bound). Georg Thieme Verlag, Stuttgart; agents for U. S. A.: Grune & Stratton, New York. 1952. Price, Kart. DM 29.70.

This is the supplementary volume No. 67 of the Archives and Atlas of the normal and pathologic anatomy presented in typical radiographs. It deals with angiography or arteriography for the recognition, treatment and evaluation of peripheral circulatory disturbances.

The presentation of the clinical entities in which arteriography and aortography may prove advantageous technic is precise and clear. In the discussion of diagnostic technics the limitations of oscillometry are emphasized. Arteriography and aortography as employed by the author are well described, in great detail and authoritatively. The diagnostic limitations and dangers are clearly presented. A brief but interesting chapter on arterio- and veno-cineradiography follows. Results of sympathectomy, arterial resection and restoration of arterial circulation through venous transplants are well documented. A concluding chapter on compensation examination is of little interest to the American reader.

One hundred and two illustrations accompany the monograph. They are excellent examples of the valuable contribution arteriography can make to the evaluation of diseases of the peripheral circulation. Their choice and reproduction are excellent. The monograph is clearly written and well printed. It should prove of value to vascular surgeons, radiologists and specialists in cardiovascular diseases.

A. G.

Hypertension: Humoral and Neurogenic Factors. Ciba Foundation Symposium. Editors for the Ciba Foundation: G. E. W. WOLSTENHOLME, O.B.E., M.A., M.B., B.Ch., and MARGARET P. CAMERON, M.A., A.B.L.S.; assisted by JOAN ETHERINGTON. 294 pages; 14 × 21 cm. Little, Brown & Co., Boston. 1954. Price, $6.75.

Under the chairmanship of Dr. Pickering this symposium brought together many of the most able investigators in the world. They presented their data concisely and the discussions were searching and to the point. Rather strong evidence was presented by Perera and Grollman that the elevation of blood pressure was but a part, and not always an essential part, of a disseminated vascular disease which we call hypertensive vascular disease.

More precise methods for detecting pheochromocytomas by measuring urinary catechol amines were presented by Goldenberg and von Euler. The search for the humoral factor or factors responsible for the vascular changes in essential hypertension continue to elude combined efforts.

This symposium is highly recommended as a splendid reference for the student of hypertension, the physiologist, the biochemist and all interested in fundamental research in this field.

S. T. R. R., JR.

Fundamentals of Clinical Cancer, with Emphasis on Early Diagnosis and Treatment. By LEONARD B. GOLDMAN, M.D. 312 pages; 17.5 × 26 cm. Grune & Stratton, New York. 1953. Price, $8.75.

This book is written as a fundamental guide to those in the practice of medicine interested in the diagnosis of cancer and its present treatment. It represents the experiences of a radiotherapist interested in the early diagnosis and the treatment of malignant disease. He draws to the attention of the reader some of the preventive methods of cancer control. He describes some of the recent methods of diagnosis and current trends in therapy.

The book is written rather simply and concisely with chapters describing the most common tumors found in the various parts of the body. The most important tumors of the head, neck, lungs, gastrointestinal and genito-urinary tract are very ably described with photographs. The material in each chapter is condensed for quick reference. A short chapter is devoted to tumors of the breast, which describes the highlights in the early diagnosis and treatment. One chapter is devoted to the most common malignant diseases of childhood.

There is at times a difference of opinion between this author and other authors regarding therapy, but this author stresses at all times the importance of early diagnosis and what to do rather than how to do it. He has tried to bring to the attention of the reader, that to suspect cancer and be wrong is pardonable, but not to suspect cancer and be wrong may be fatal.

E. H. S., JR.

BOOKS RECEIVED

Books received during February are acknowledged in the following section. As far as practicable those of special interest will be selected for review later, but it is not possible to discuss all of them.

Adrenal Cortex: Transactions of the Fifth Conference, November 4, 5 and 6, 1953, Princeton, N. J. Edited by ELAINE P. RALLI, M.D., Associate Professor of Medicine, New York University College of Medicine, New York, N. Y. 187 pages; 23.5 × 16 cm. 1954. Sponsored by the Josiah Macy, Jr. Foundation, New York, N. Y. Price, $3.75.

Behandlung Rheumatologischer Erkrankungen Durch Anästhesie. By DOZENT DR. MED. EGON FENZ. 112 pages; 22 × 14.5 cm. (paper-bound). 1955. Verlag von Dr. Dietrich Steinkopff, Darmstadt. Price, kart. 12.–

Clinical Diagnosis. By ELMER G. WAKEFIELD, B.S.A., B.Sc., M.D., F.A.C.P., Diplomate of the American Board of Internal Medicine, Consulting Physician, Section of Medicine, Mayo Clinic and Associate Professor of Medicine, Mayo Foundation for Medical Education and Research, Graduate School, University of Minnesota, Rochester, Minnesota. 1,611 pages; 25.5 × 17 cm. 1955. Appleton-Century-Crofts, Inc., New York. Price, $22.50.

The Clinical Examination of the Nervous System. 10th Ed. By G. H. MONRAD-KROHN, M.D., F.R.C.P., Professor of Medicine in the University of Oslo, etc. 428 pages; 22 × 14.5 cm. 1955. Paul B. Hoeber, Inc., Medical Book Department of Harper & Brothers, New York. Price, $7.50.

The Coagulation of Blood: Methods of Study. Edited by LEANDRO M. TOCANTINS, M.D. Prepared with the help and under the sponsorship of the Panel on Blood Coagulation of the Committee on Medicine and Surgery of the National Academy of Sciences, National Research Council. 240 pages; 23.5 × 15.5 cm. 1955. Grune & Stratton, New York. Price, $5.75.

Connective Tissues: Transactions of the Fifth Conference, February 8, 9, and 10, 1954, Princeton, N. J. Edited by CHARLES RAGAN, M.D., Associate Professor of Medicine, Columbia University College of Physicians and Surgeons, New York, N. Y. 222 pages; 24 × 15.5 cm. 1954. Sponsored by the Josiah Macy, Jr. Foundation, New York, N. Y. Price, $4.25.

Diabetes Mellitus in Infants and Children: Report of the Twelfth M & R Pediatric Research Conference. 79 pages; 23 × 15 cm. (paper-bound). 1955. M & R Laboratories, Columbus, Ohio. No charge.

Further Observations on Some Little Known Tropical and Subtropical Diseases, Internal, Surgical and Cutaneous: Monograph. By ALDO CASTELLANI, M.D., F.R.C.P. (London), F.A.C.P. (U. S. A.), Professor in the Institute for Tropical Diseases, Lisbon, etc. 292 pages; 25 × 19 cm. (paper-bound). 1954. Instituto de Medicina Tropical de Lisboa, Lisbon. Price, $2.00.

Medical Greek and Latin at a Glance. 3d Ed. By WALTER R. AGARD, B.Litt. (Oxon.), Professor of Classics, University of Wisconsin; and HERBERT M. HOWE, Ph.D., Associate Professor of Classics, University of Wisconsin. 96 pages; 24.5 × 15.5 cm. 1955. Paul B. Hoeber, Inc., Medical Book Department of Harper & Brothers, New York. Price, $1.85.

Orientamenti Diagnostici e Terapeutici Attuali Nella Chirurgia Della Milza. By G. BENDANDI. 128 pages; 24.5 × 17 cm. (paper-bound). 1954. Edizioni Mediche e Scientifiche, Rome.

Peripheral Vascular Diseases. 2nd Ed. By EDGAR V. ALLEN, B.S., M.A., M.D., M.S. in Medicine, F.A.C.P., Section of Medicine, Mayo Clinic, Professor of Medicine, Mayo Foundation, Graduate School, University of Minnesota, etc.; NELSON W. BARKER, B.A., M.D., M.S. in Medicine, F.A.C.P., Section of Medicine, Mayo Clinic, Professor of Medicine, Mayo Foundation, Graduate School, University of Minnesota; and EDGAR A. HINES, JR., B.S., M.A., M.D., M.S. in Medicine, F.A.C.P., Section of Medicine, Mayo Clinic, Professor of Medicine, Mayo Foundation, Graduate School, University of Minnesota; with Associates in the Mayo Clinic and Mayo Foundation. 825 pages; 24 × 16 cm. 1955. W. B. Saunders Company, Philadelphia. Price, $13.00.

Potassium Metabolism in Health and Disease. Modern Medical Monographs 12. By HOWARD L. HOLLEY, M.D., Department of Medicine, University of Alabama Medical-Dental Schools, Birmingham, Alabama; and WARNER W. CARLSON, Ph.D, Department of Biochemistry, University of Alabama Medical-Dental Schools, Birmingham, Alabama. 131 pages; 22 × 14 cm. 1955. Grune & Stratton, New York. Price, $4.50.

Progress in Allergy. Volume IV. Contributors: M. G. BOHROD, Rochester, N. Y.; TH. F. DOUGHERTY, Salt Lake City, Utah; F. L. ENGEL, Durham, N. C.; K. MAUNSELL, London; R. L. MAYER, Summit, N. J.; B. NOELPP, Basel; I. NOELPP-ESCHENHAGEN, Basel; G. PINCUS, Shrewsbury, Mass.; and S. RAFFEL, Stanford, Calif.; edited by PAUL KALLÓS, Helsingborg. 520 pages; 25 × 17 cm. 1955. Little, Brown and Company, Boston. Price, $20.00.

Reactions with Drug Therapy. By HARRY L. ALEXANDER, M.D., Emeritus Professor of Clinical Medicine, Washington University Medical School, etc. 301 pages; 24 × 16 cm. 1955. W. B. Saunders Company, Philadelphia. Price, $7.50.

Tumors of the Major Salivary Glands (*Atlas of Tumor Pathology, Section IV, Fascicle 11*). By FRANK W. FOOTE, JR., M.D., Attending Pathologist, Memorial Center for Cancer and Allied Diseases, New York, New York, etc.; and EDGAR L. FRAZELL, M.D., Associate Attending Surgeon, Memorial Center for Cancer and Allied Diseases, New York, New York. 149 pages; 26 × 20 cm. (paper-bound). 1954. Published by the Armed Forces Institute of Pathology under the auspices of the Subcommittee on Oncology of the Committee on Pathology of the National Research Council, Washington, D. C. Price, $1.50; for sale by the American Registry of Pathology, Armed Forces Institute of Pathology, Washington, D. C.

Tumors of the Retroperitoneum, Mesentery and Peritoneum (*Atlas of Tumor Pathology, Section VI, Fascicles 23 and 24*). By LAUREN V. ACKERMAN, M.D., Professor of Pathology and Surgical Pathology, Washington University School of Medicine, etc. 136 pages; 26 × 20 cm. (paper-bound). 1954. Published by the Armed Forces Institute of Pathology under the auspices of the Subcommittee on Oncology of the Committee on Pathology of the National Research Council, Washington, D. C. Price, $1.50; for sale by the American Registry of Pathology, Armed Forces Institute of Pathology, Washington, D. C.

Tumors of the Soft Tissues (*Atlas of Tumor Pathology, Section II, Fascicle 5*). By ARTHUR PURDY STOUT, M.D., Professor of Pathology, Columbia University, College of Physicians and Surgeons, New York City. 138 pages; 26 × 20 cm. (paper-bound). 1953. Published by the Armed Forces Institute of Pathology under the auspices of the Subcommittee on Oncology of the Committee on Pathology of the National Research Council, Washington, D. C. Price, $2.00; for sale by the American Registry of Pathology, Armed Forces Institute of Pathology, Washington, D. C.

Tumors of the Stomach (*Atlas of Tumor Pathology, Section VI, Fascicle 21*). By ARTHUR PURDY STOUT, M.D., Professor of Pathology, Columbia University, College of Physicians and Surgeons, New York City. 104 pages; 26 × 20 cm. (paper-bound). 1953. Published by the Armed Forces Institute of Pathology under the auspices of the Subcommittee on Oncology of the Committee on Pathology of the National Research Council, Washington, D. C. Price, $1.75; for sale by the American Registry of Pathology, Armed Forces Institute of Pathology, Washington, D. C.

Viral and Rickettsial Diseases of the Skin, Eye and Mucous Membranes of Man. By HARVEY BLANK, M.D., Squibb Institute for Medical Research, etc.; and GEOFFREY RAKE, M.B., B.S., University of Pennsylvania, etc.; with a foreword by DONALD M. PILLSBURY, M.D., University of Pennsylvania. 285 pages; 24.5 × 16 cm. 1955. Little, Brown and Company, Boston. Price, $8.50.

COLLEGE NEWS NOTES

New Life Members

It is indeed a pleasure for the College to announce that the following Fellows have become Life Members since the publication of the list in last month's issue of this journal:

Dr. Charles Edward Hamilton, Brooklyn, N. Y.
Dr. Walter deM. Scriver, Montreal, Que., Can.
Dr. Samuel M. Browne, Clemson, S. C.
Dr. Lucien Young Dyrenforth, Jacksonville, Fla.
Dr. Maurice Roberts Moore, Norwich, Conn.
Dr. James W. Haviland, Mercer Island, Wash.
Dr. Joseph M. Barker, Beverly Hills, Calif.
Dr. Jack L. Eisaman, Bluffton, Ind.
Dr. Elmer S. Robertson, Richmond, Va.
Dr. G. Richards Williamson, New Orleans, La.
Dr. Charles Collins Orr, Asheville, N. C.
Dr. Harry A. Solomon, New York, N. Y.
Dr. D. C. Burkes, Portland, Ore.
Dr. R. Manning Clarke, National City, Calif.
Dr. James F. Gleason, Atlantic City, N. J.
Dr. James K. Fancher, Atlanta, Ga.
Dr. L. Rush Lambert, Fairmont, W. Va.
Dr. J. Lloyd Morrow, Passaic, N. J.
Dr. Milton J. Raisbeck, New York, N. Y.
Dr. David Greer, Houston, Tex.
Dr. A. Cameron MacNiel, Shaker Heights, Ohio
Dr. James Joseph Short, Glendale, Calif.
Dr. Marion D. Hargrove, Shreveport, La.

Gifts to College Library of Publications by Members

The College is sincerely grateful to the following members who have presented copies of their books, in most instances autographed, to the College Library of Publications by Members:

Allen E. Hussar, M.D., F.A.C.P., Montrose, N. Y., and Howard L. Holley, M.D., F.A.C.P., Birmingham, Ala.—*Antibiotics and Antibiotic Therapy—A Clinical Manual.*

C. A. D'Alonzo, M.D., F.A.C.P., Wilmington, Del.—*Modern Occupational Medicine,* with A. J. Fleming, M.D., and J. A. Zapp, Ph.D.

John H. Bland, M.D. (Associate), Burlington, Vt.—*The Clinical Use of Fluid and Electrolyte.*

A.C.P. Members to Be Guests of Sharp & Dohme for Symphony Concert

Sharp and Dohme, Inc., Division of Merck & Co., Inc., Philadelphia, has underwritten the Symphony Concert to be presented by the famed Philadelphia Orchestra at Philadelphia on Monday evening, April 25, the opening day of the Thirty-Sixth Annual Session of the College. Contrary to the announcement in the Annual Session Program, tickets will be available, two to a member, on a purely complimentary basis.

Formal invitations and reservations forms have been mailed to all members. Tickets will be available also to other registrants at the meeting.

Coming A.B.I.M. Examinations

The American Board of Internal Medicine, William A. Werrell, M.D., Executive Secretary-Treasurer, 1 W. Main St., Madison 3, Wis.

Written examinations to be held Oct. 17 in selected centers. Closing date for applications is May 1.

The following oral examinations have been scheduled:

Philadelphia—May 4–5	Portland, Ore.—Sept. 14–16
Washington, D. C.—May 6–7	Chicago—Nov. 30–Dec. 2

In addition, an oral examination in the sub-specialty of Cardiovascular Disease will be held in Chicago, Nov. 30; the closing date for applications is June 1.

A.C.P. Regional Meetings

HAWAII Regional Meeting, Honolulu, T. H., February 10, 1955; Dr. Nils P. Larsen, F.A.C.P., Honolulu, Governor. Dr. William D. Stroud, F.A.C.P., Philadelphia, Treasurer of the College, was the special guest and presented a new film on arteriosclerosis, with most of the program devoted to a consideration of hypertension. Twenty-six physicians were in attendance.

VIRGINIA Regional Meeting, Lynchburg, Va., February 24, 1955; Dr. C. M. Caravati, F.A.C.P., Richmond, Governor; Dr. Alex F. Robertson, Jr., F.A.C.P., Staunton, Chairman of the Virginia Section; Dr. James F. Waddill, F.A.C.P., Norfolk, Secretary-Treasurer of Virginia Section; Dr. George B. Craddock, F.A.C.P., Lynchburg, Chairman of the Program Committee. President Cyrus C. Sturgis delivered the banquet address at the Virginian Hotel. A large and representative group was in attendance. The program was exceptionally well received. The attendance figures were not available at the time of preparation of this note.

NEBRASKA Regional Meeting, Omaha, Nebr., February 26, 1955; Dr. Joseph D. McCarthy, F.A.C.P., Omaha, Governor; Dr. Willis D. Wright, F.A.C.P., Omaha, Chairman of the Program Committee. Dr. Marion A. Blankenhorn, Cincinnati, First Vice President of the College, presented a paper on the scientific session, and at the banquet spoke on "The American College of Physicians as a Postgraduate Medical Institution." Mr. E. R. Loveland, Executive Secretary, Philadelphia, also addressed the banquet, his subject being "What's New in the College?". There was an excellent scientific program but weather conditions were so unfavorable and hazardous that the attendance was less than customary. The Fellows in attendance adopted a special resolution in recognition of the nine years of efficient service rendered to the State of Nebraska by Dr. McCarthy who retires as the College Governor in April. The attendance figures were not available at the time of preparation of this note.

UTAH Regional Meeting, Salt Lake City, Utah, March 5, 1955; Dr. T. C. Bauerlein, F.A.C.P., Salt Lake City, Governor. Speakers at the banquet included Dr. George F. Strong, F.A.C.P., Vancouver, President-Elect of the College, and Dr. Fuller B. Bailey, F.A.C.P., Salt Lake City, Regent of the College. The scientific program was an exceptionally attractive one. The attendance figures were not available at the time of preparation of this note.

KANSAS Regional Meeting, Wichita, Kans., March 18–19, 1955; Dr. William C. Menninger, F.A.C.P., Topeka, Governor; Dr. James B. Fisher, F.A.C.P., Wichita, Chairman of the Program Committee; Dr. LeRoy H. Sloan, F.A.C.P., Chicago,

Past President of the College, was the honored guest speaker at the banquet. The attendance figures were not available at the time of preparation of this note.

TENNESSEE Regional Meeting, Chattanooga, Tenn., April 11, 1955; Dr. R. H. Kampmeier, F.A.C.P., Nashville, Governor; Dr. Sam A. Overstreet, F.A.C.P., Governor for Kentucky, was the special guest. This meeting was held during the afternoon of a day during the Tennessee State Medical Association meeting. One of the primary purposes of the meeting was the consideration of organizational plans for future meetings and also to discuss with the Governor for Kentucky the possibilities of a Kentucky-Tennessee Joint Regional Meeting in the future. A formal luncheon was held and a half-day of scientific papers was presented.

Postgraduate Course, Electrocardiographic Analysis

Dr. Leslie French, F.A.C.P., Washington, is directing a Postgraduate Course in Electrocardiographic Analysis at the Heart Station of the Prince Georges General Hospital at Cheverly, Md., the Course being held from 8:30 to 10:30 in the evenings of Fridays throughout the months of February and March, 1955. The Course attempts to inform qualified physicians regarding recent advances in the realm of Electrocardiography and the Practical Analysis of Electrocardiograms. It consists of lectures, demonstrations, round-table conferences and supervised practical analysis exercises. The fee, $20.00, includes mimeographed outline of the Course.

Scholarship in Dermatology and Syphilology

A three-year scholarship in dermatology and syphilology is announced by Dr. Marion B. Sulzberger, F.A.C.P., Professor and Chairman of the Department of Dermatology and Syphilology of the New York University Post-Graduate Medical School, a unit of New York University-Bellevue Medical Center.

The scholarship, which pays $3,000.00 per annum, plus tuition, is open to graduates of approved medical schools who have completed one year of acceptable internship. Recipients will be selected on the basis of academic background and character. Experience in one of the basic sciences is considered desirable but not essential.

Applicants should include a transcript and other pertinent data from the medical school from which they graduated, a letter of recommendation from the dean, and one from the individual responsible for their internship. At least one other letter of recommendation is required.

No applications will be accepted after May 31, 1955, for the class beginning the following Oct. 1. Applications should be sent to the Dean of the Post-Graduate Medical School, 550 First Ave., New York 16, N. Y.

Residencies in Psychiatry

The Veterans Administration Hospital, Lyons, N. J., has available residencies in psychiatry for a one- to three-year period which are fully accredited by the American Board of Psychiatry and Neurology. The training program consists of lectures, conferences and seminars under the direction of the Department of Psychiatry, New York Medical College, and offers intensive training, both intramurally and through rotation in special hospitals and clinics in the adjacent area. There is, in addition, a series of extensive guest lecturers as well as an Annual Institute at the Hospital. Training may commence at any time. Further details may be obtained from C. N. Baganz, M.D., F.A.C.P., Veterans Administration Hospital, Lyons, N. J.

Meetings of International Medical Interest

Meeting Dates and Locations	*Details*
May 26–31, Lausanne, Switzerland International Congress of Comparative Pathology	Professor Hauduroy, Secretary General 19 Rue Cesar Roux Lausanne, Switzerland.
June 1–4, London, England British Medical Association	Dr. A. Macrae, Secretary B.M.A. House Tavistock Square London, W.C.1, England.
June 13–17, Scheveningen, The Hague, Netherlands European Congress on Rheumatism	Dr. H. van Swaay, Secretary Pieter Bothstraat 12 The Hague, Netherlands.
June 18–19, Stockholm, Sweden Congress of the International Association for the Study of the Bronchi	Dr. J. M. Lemoine 187 Boulevard St. Germain Paris 7e, France.
June 20–22, Toronto, Canada Canadian and British Medical Associations	Dr. Arthur D. Kelly, General Secretary 244 St. George St. Toronto, Canada.
June 21–25, London, England Commonwealth Health and Tuberculosis Conference	Mr. J. H. Harley Williams Secretary General Tavistock House North Tavistock Square London, W.C.1, England.
July 4–8, Cambridge, England Congress of International Diabetes Federation	Mr. James G. L. Jackson Executive Secretary General 152 Harley St. London, W.1, England.
July 18–23, London, England Congress of International Association of Applied Psychology	Dr. C. B. Frisby, President 14 Welbeck St. London, W.1, England.
Aug. 20–27, Sydney, Australia Australasian Medical Congress	Federal Council of the B.M.A in Australia 135 Macquaire St. Sydney, N.S.W., Australia.
Sept. 1–4, Verona, Italy International Medical Congress	Offices of the International Verona Fair Piazza Bra. Verona, Italy.
Sept. 2–, Fribourg, Switzerland International Congress of Angiology and Histopathology	Dr. Gerson 4 Rue Pasquier Paris 8e, France.
Sept. 20–26, Vienna, Austria World Medical Association	Dr. Louis H. Bauer, Secretary-General 345 East 46th St. New York 17, N. Y.

Nov. 6–12, Rio de Janeiro, Brazil International Congress of Allergology	Dr. Bernard N. Halpern Secretary General 197 Boulevard St. Germain Paris 7e, France.
Nov. 18–26, Caracas, Venezuela Venezuelan Congress of Medical Sciences	Dr. A. L. Briceno Rossi Secretary General Apartado 4412 Ofic. del Este Caracas, Venezuela.

Dr. Anton J. Carlson, M.A.C.P., Chicago, was unanimously elected Honorary President for Life of the National Society for Medical Research at the Society's annual meeting in Chicago on Feb. 6. President of the Society since its organization in 1946, Dr. Carlson relinquishes the active leadership to Dr. Lester R. Dragstedt, F.A.C.P., Chairman of the Department of Surgery at the University of Chicago.

Dr. Donald M. Pillsbury, F.A.C.P., Philadelphia, has been appointed Director of the recently organized Commission on Cutaneous Diseases of the Armed Forces Epidemiological Board. The organizational meeting of the Commission was held in Philadelphia Feb. 17–18.

Dr. William C. Voorsanger, F.A.C.P., Emeritus Chief of Medicine and Diseases of the Chest at Mount Zion Hospital, San Francisco, was recently awarded a certificate of merit in recognition of his fifty years of service on the hospital staff. At the same time, Dr. Voorsanger was told that a fund named in his honor had been created to further the study of pulmonary diseases. A Founder and former President of the California Tuberculosis Association and a past President of the National Tuberculosis Association, Dr. Voorsanger has been a Fellow of the American College of Physicians since 1917, having graduated from Cooper Medical College in 1899.

Dr. Alphonse McMahon, F.A.C.P., St. Louis, has been honored by the Alumni Association of the St. Louis College of Pharmacy and Allied Sciences for his "distinguished service to medicine and pharmacy." The honor was conferred on Dr. McMahon at the annual Awards Dinner Dance of the Association on Feb. 27.

Dr. Lemuel C. McGee, F.A.C.P., Wilmington, College Marshal and Governor for Delaware, has been appointed to the new fifteen-member Medical Advisory Committee of the Social Security Administration. The new Committee will help establish guides and procedures for determining medical evidence as to existence and extent of disability.

Drs. F. Janney Smith, F.A.C.P., Detroit, and William A. Brams, F.A.C.P., Chicago, participated in a Symposium on The Management of Acute Myocardial Infarction, presented by the Medical Society of Milwaukee County on Feb. 10. Their respective subjects were "The Place of Anti-Coagulants" and "General Clinical Management."

Speaking on "Renal Aspects of the Pathogenesis of Hypertension," Dr. Irvine H. Page, F.A.C.P., Cleveland, participated in a joint meeting of the North Central Region of the College of American Pathologists and of the Michigan Pathological Society, which was held in Detroit, Feb. 12. In addition, Dr. Page was a co-author

of "Kidney Function in Disease" with Drs. Arthur C. Corcoran, Cleveland, and Don Carlos Hines (Associate), Indianapolis.

"Summary of the Clinical Aspects of Bioflavonoids and Ascorbic Acid" was the topic of a talk given by Dr. John B. Youmans, F.A.C.P., Nashville, Tenn., at an all-day conference on "Bioflavonoids and the Capillary," held in New York City, Feb. 11, under the auspices of the New York Academy of Sciences.

Dr. Joseph B. Vander Veer, F.A.C.P., Philadelphia, discussed "The Management of Patients Severely Ill with Acute Myocardial Infarction" at a Symposium on the Management of Coronary Artery Disease, jointly sponsored by the Hartford (Conn.) Heart Association and the Hartford Hospital on Feb. 17. Moderator of the Symposium was Dr. John C. Leonard, F.A.C.P., Director of Medical Education of the Hospital and College Governor for Connecticut.

Drs. Elmer C. Bartels, F.A.C.P., and William Dameshek, F.A.C.P., both of Boston, and Dr. Arthur M. Master, F.A.C.P., New York City, were among the guest speakers at the joint meeting of the Atlanta Graduate Medical Assembly and the Southeastern Surgical Congress, which convened Feb. 21–24 in Atlanta, Ga. In addition, Dr. Bartels, together with Dr. Edgar S. Gordon, F.A.C.P., Madison, Wis., participated in a Symposium on Arthritis and Allied Diseases, and Dr. Master, together with Drs. Herrman L. Blumgart, F.A.C.P., and Robert W. Wilkins, F.A.C.P., both of Boston, collaborated in a Symposium on Angina Pectoris that was presided over by Dr. Eugene B. Ferris, F.A.C.P., Atlanta, College Regent. Dr. Burgess L. Gordon, F.A.C.P., Philadelphia, took part in a Symposium on Cancer of the Lung.

Dr. Richard W. Vilter, F.A.C.P., Cincinnati, participated in both a Symposium on Obstetrics and a Panel on Obstetrics during the Twentieth Annual Midwinter Postgraduate Clinics, sponsored by the Colorado State Medical Society and held in Denver, Feb. 15–18. During the meeting Dr. Francis R. Manlove, F.A.C.P., Denver, addressed the dinner Tuesday night on the subject of "The Role of the Medical Center in the Community."

Speaking on "Growth in Animal Lung Tumors," Dr. Michael B. Shimkin, F.A.C.P., Bethesda, Md., participated in a Symposium on Growth in Chicago on Feb. 9. The Symposium was sponsored by the Sigma Xi Club of the Chicago Medical School.

Dr. Sydney G. Margolin, F.A.C.P., New York City, discussed "Psychosomatic Approach in Medicine" on Feb. 28 at the Connecticut State Hospital in Middletown. His lecture was one of those delivered during the Eighth Connecticut Postgraduate Seminar in Psychiatry and Neurology.

Dr. Edward L. Bortz, F.A.C.P., Philadelphia, College Regent, spoke on "Industry and the Senior Citizen" at the annual meeting of the American Academy of Occupational Medicine, held in Philadelphia, Feb. 10–11. Other participants and their subjects included Dr. Joseph T. Beardwood, Jr., F.A.C.P., Philadelphia, "Early Diagnosis: The Industrial Physician's Duty and Opportunity" and Dr. C. Anthony D'Alonzo, F.A.C.P., Wilmington, Del., "Some Aspects of Hypertension in Industry."

Four members of the College will be among the out-of-state speakers at the 163rd Annual Meeting of the Connecticut State Medical Society, to be held in Stratford, April 26–28. Dr. Frederic D. Zeman, F.A.C.P., New York City, will discuss "Practical Problems and Clinical Errors in the Care of the Aged," and Dr. Harold D. Levine, F.A.C.P., Boston, will present "Non-Specificity of the Electro-Cardiogram in Coronary Artery Disease." Dr. Gene H. Stollerman (Associate), Irvington-on-Hudson, N. Y., is scheduled to speak on "Hormones in Management of Rheumatic Fever," and Dr. Claude-Starr Wright, F.A.C.P., Columbus, Ohio, will consider "Indications for Splenectomy."

Dr. Albert Milzer, F.A.C.P., Chicago, discussed "Studies on Active Immunization with Noninfectious Vaccines" at the Conference on Biology of Poliomyelitis of the New York Academy of Sciences, held in New York City, Jan. 20–21.

Dr. Herrman L. Blumgart, F.A.C.P., Boston, delivered a talk on "The Heart and the Thyroid" under the auspices of the Heart Association of Greater Miami on Feb. 24. During his Florida visit, Dr. Blumgart also conducted grand rounds at the Jackson Memorial Hospital, Miami, and lectured on "Heart Block" to the first-year medical students at the University of Miami School of Medicine, Coral Gables.

Dr. Howard F. Polley, F.A.C.P., Rochester, Minn., discussed "Medical Management and Physical Treatment of Rheumatoid Arthritis" at a joint meeting of the Chicago Rheumatism Society and the Chicago Society of Physical Medicine and Rehabilitation on Feb. 23 at the Stritch School of Medicine of Loyola University.

Dr. James L. McCartney, F.A.C.P., Garden City, N. Y., returned last month from a world cruise during which he addressed, under the auspices of the World Medical Association, medical societies in Cuba, Japan, Philippine Islands, Ceylon, India, Pakistan, and Italy. Dr. McCartney's topic was "Treatment of the Involutional and Senile Psychoses," and he also inspected the psychiatric facilities in the countries visited.

Dr. W. Barry Wood, Jr., F.A.C.P., St. Louis, spoke on "Acute Bacterial Pneumonia" at the Veterans Administration Center, Des Moines, Iowa, on Feb. 21.

Five members of the College are contributing to the Third Annual Scientific Assembly of the West Virginia Academy of General Practice, which convenes in Charleston, April 16–17. Speakers scheduled for Saturday afternoon include Dr. Charles A. Doan, F.A.C.P., Columbus, Dean and Professor of Medicine, Ohio State University College of Medicine and A.C.P. Governor for Ohio; Dr. Theodore E. Woodward, F.A.C.P., Baltimore, Professor of Medicine and Head of the Department, University of Maryland School of Medicine; Dr. Edward W. Lowman (Associate), New York City, Director of Inpatients, Institute of Physical Medicine and Rehabilitation; Dr. E. Perry McCullagh, F.A.C.P., Cleveland, Head of Section, Department of Endocrinology and Metabolism, Cleveland Clinic; and Dr. E. Hugh Luckey, F.A.C.P., New York City, Dean and Associate Professor of Medicine, Cornell University Medical College.

Dr. William G. Leaman, Jr., F.A.C.P., Philadelphia, was a guest speaker at the Alumni Postgraduate Meeting of the College of Medical Evangelists, held in Los Angeles, Feb. 15–17. His subjects were "Preventive Measures of Importance in Heart Disease," "The Management of Congestive Failure," "Cardiac Conditions

Complicating Obstetrical Care," "Coronary Heart Disease," and "The Therapeutic Use of Whole Blood."

On Feb. 8 Dr. Leaman addressed the San Diego County Medical Society on "Long Survival in Coronary Heart Disease with Special Reference to Management."

Dr. Garfield G. Duncan, F.A.C.P., Philadelphia, recently participated in the International Medical Assembly of Southwest Texas in San Antonio, giving lectures on "Diabetic Management in General Practice," "Newer Insulin Preparations," and "Treatment of Hypertension." Dr. Duncan also participated in a panel discussion dealing with "Diseases of the Gall Bladder and Complications of Diabetes."

Drs. Tinsley R. Harrison, F.A.C.P., Birmingham, Ala., and William A. Sodeman, F.A.C.P., Columbia, Mo. (Internal Medicine), were among the guest speakers at the Eighteenth Annual Meeting of the New Orleans Graduate Medical Assembly, held March 7–10. Dr. Joseph B. Kirsner, F.A.C.P., Chicago (Gastroenterology), also contributed to the program.

Dr. Robert J. Rohn (Associate), Indianapolis, Ind., spoke on "Hematological Observations in Acute Disseminated Lupus Erythematosis" at the University of Wisconsin, Madison, on Feb. 15.

Dr. Michael B. Shimkin, F.A.C.P., Bethesda, Md., considered "Chemotherapy of Lymphomas: Effect upon Survival" at the Tumor Clinic Conference held at the Harlem Hospital, New York City, Feb. 16.

Dr. Philip K. Bondy (Associate), New Haven, Conn., addressed the Norfolk District Medical Society in Boston, Feb. 15. His topic was "Studies of Lipid Metabolism in Man."

Dr. Thomas A. Warthin, F.A.C.P., Boston, spoke on "Gastrointestinal Bleeding" at the Hartford (Conn.) Medical Society on March 21. Dr. Louis A. Soloff, F.A.C.P., Philadelphia, is scheduled to give the weekly lecture on April 18, his subject being "Medical Aspects of Mitral Commissurotomy."

Dr. Bernard J. Alpers, F.A.C.P., Professor of Neurology at Jefferson Medical College of Philadelphia, was one of the guest lecturers at the Seventh Annual Institute in Psychiatry and Neurology, held at the Veterans Administration Hospital, North Little Rock, Ark., Feb. 24–25.

Under the Presidency of Dr. John M. Sheldon, F.A.C.P., Ann Arbor, Mich., the American Academy of Allergy held its Eleventh Annual Meeting in New York City, Feb. 7–9. Dr. Homer E. Prince, F.A.C.P., Houston, Tex., President of the American College of Allergists, discussed "Common Sense Allergy," and Dr. Samuel M. Feinberg, F.A.C.P., Chicago, presided over the Ciba Seminar, "Recent Advances in Hypersensitivity."

Dr. James F. Hays, F.A.C.P., formerly a Captain in the Medical Corps of the U. S. Navy, has now retired (as of September, 1954) and has accepted an appointment as Medical Director of the International Latex Corp. at Dover, Del.

Dr. James C. Metts, F.A.C.P., Savannah, was recently elected the first President of the Staff of the new Memorial Hospital of Chatham County. The $4,500,000 hospital is expected to be ready to receive patients by July 1.

Dr. Kelso A. Carroll, F.A.C.P., has recently been appointed Manager of the Veterans Administration Center at Bay Pines, Fla. Dr. Carroll was formerly Assistant Chief Medical Director for Planning in the Veterans Administration Department of Medicine and Surgery, Washington, D. C.

Dr. Cole B. Gibson, F.A.C.P., Meriden, Conn., who retired as Superintendent and Medical Director of Undercliff Sanatorium last June, has recently been appointed Acting Director of Bradley Memorial Hospital, Southington. A former President of the Connecticut State Medical Society, Dr. Gibson had been Superintendent at Undercliff since 1919.

Dr. James M. Faulkner, F.A.C.P., Dean and Professor of Clinical Medicine at Boston University School of Medicine, will become Medical Director of the Massachusetts Institute of Technology at the conclusion of the present academic year. Dr. Faulkner, however, will continue his teaching and administrative positions with the School of Medicine.

Dr. John Z. Bowers, F.A.C.P., heretofore Dean and Professor of Radiobiology at the University of Utah College of Medicine, Salt Lake City, has been named to succeed Dr. William S. Middleton, M.A.C.P., as Dean of the University of Wisconsin Medical School. Dr. Middleton became Chief Medical Director of the Veterans Administration on March 1.

Dr. Oswald T. Avery, first recipient (1932) of the John Phillips Memorial Award of the American College of Physicians, died of cancer at the Vanderbilt University Hospital, Nashville, Tenn., on February 20, 1955, at the age of 77.

Dr. Avery received the Award, $1,500.00, for the series of studies upon the Pneumococcus in which he played a leading rôle, beginning with the discovery of the type-specific soluble capsular polysaccharides and culminating in the discovery of a bacterium producing an enzyme which splits the polysaccharides of Type 3 Pneumococcus in vitro, thus rendering it susceptible to phagocytosis and thereby protecting the animals infected with it.

Dr. S. M. Poindexter, F.A.C.P., Boise, Idaho, is President of the Southwestern Idaho District Medical Society and a member of the National Board of Medical Examiners. Dr. Poindexter is a former Governor of the American College of Physicians.

Dr. George F. Strong, F.A.C.P., President of the American College of Physicians, addressed the Southwestern Idaho District Medical Society meeting, March 3, 1955, while en route to Salt Lake City, where he addressed the Utah Regional Meeting of the American College of Physicians on March 5.

OBITUARIES

DR. GEORGE E. BAKER

It is with a great deal of regret that the members of the Montana-Wyoming Region of the American College of Physicians record the death of Dr. George Erwin Baker, F.A.C.P., of Casper, Wyo., who died Dec. 18, 1954, of coronary thrombosis and myocardial infarction.

Dr. Baker was born in O'Neill, Nebr., Feb. 20, 1905. After the usual preliminary studies, he attended Washington University in St. Louis. He received an A.B. degree from the University of Wyoming in 1928 and an M.D. degree from the University of Nebraska College of Medicine in 1931. He interned at St. Mary's Infirmary and Mount St. Rose Sanatorium in St. Louis, 1931–32. He was a resident at the Caledonian Hospital in Brooklyn in 1932.

Dr. Baker joined the staff of the Memorial Hospital of Natrona County in Casper in 1932 and later became Chief of the Medical Section and Chief of Staff. He was Natrona County Health Officer and Registrar of Vital Statistics from 1938–41. He was a former member of the Board of Trustees of the Wyoming Medical Service, President of the Natrona County Medical Society in 1945–46, and President of the Wyoming State Medical Association, 1948–49.

Dr. Baker was a Diplomate of the American Board of Internal Medicine, a member of Sigma Xi and became a Fellow of the American College of Physicians in 1941.

Practicing in an area where Rocky Mountain Spotted Fever was prevalent and where many cases of this disease were very severe, he early began to study these cases carefully and to report them. Trying out different methods of treatment that were in use at that time, he became a national authority on Rocky Mountain Spotted Fever. This was, of course, in a day before antibiotics made the treatment of Rickettsial diseases comparatively simple. Dr. Baker published numerous articles on Spotted Fever and wrote the section on this disease in Tice's *Symptoms of Medicine.*

His practice and his studies are a fine example of good clinical research being done in a more or less sparsely populated State far from the nearest medical school or medical center, and it is to his credit that he carried on such splendid work under these circumstances. In 1951 Dr. Baker took further postgraduate work at the Cook County Postgraduate School of Medicine in Cook County Hospital, and since that time had devoted more and more of his time to cardiology.

He was active in the American College of Physicians in Montana and Wyoming and was always a friendly and coöperative colleague. Our distances in this region are so great as to have made it impossible for him to attend all of our regional meetings, but we were always able to call on him for help in the affairs of the College.

The members of the Montana-Wyoming Region, as well as his host of friends throughout the country, remember Dr. Baker with much kindliness and extend their sincerest sympathy to his young family.

HAROLD W. GREGG, M.D., F.A.C.P.,
Governor for Montana and Wyoming

DR. GERDON E. BAKER

We record with regret the sudden death of Gerdon Edward Baker, M.D., F.A.C.P., at his home in Forty Fort, Pa., on Jan. 10, 1955.

Born in Noxen, Pa., Dec. 5, 1879, Dr. Baker attended Bloomsburg Normal School and taught for ten years in a private preparatory school. Finally his long-standing ambition was satisfied in 1915, when he received an M.D. degree from the Medico-Chirurgical College of Philadelphia. For many years, he played an active and important part in the medical life of Luzerne County. An Associate in Medicine from 1917–19, he was made Chief of Medical Service of the Wilkes-Barre General

Hospital in 1919. He filled this position with distinction until 1942 when he became Head of the Department of Medicine. This position he continued to hold until 1954.

He was a member of the Luzerne County and Lehigh Valley Medical Societies, the Medical Society of the State of Pennsylvania, and the American Medical Association. Dr. Baker was a Diplomate of the American Board of Internal Medicine and had been a Fellow of the American College of Physicians since 1927.

THOMAS M. MCMILLAN, M.D., F.A.C.P.,
Governor for Eastern Pennsylvania

DR. RAYMOND L. BARRETT, SR.

On the night of Dec. 10, 1954, Dr. Raymond Lathrop Barrett, Sr., F.A.C.P., died at his home in Springfield, Mass.

Born in Millerton, N. Y. June 21, 1894, Dr. Barrett obtained his Bachelor of Science degree from Dartmouth College in 1918 and his Doctorate in Medicine from Columbia University College of Physicians and Surgeons in 1921. Between 1922 and 1923 he served a rotating internship at the Brooklyn (N. Y.) Hospital. In 1923 he established his practice in Springfield, where he became identified with the Springfield Hospital; in 1949 he became Chief of the Department of Medicine at that hospital and in 1951 he was named Consultant to the Medical Service. Subsequent to 1934 he had devoted his major interest and efforts to the field of gastroenterology, and he was Consultant in Gastroenterology to the Health Department Hospital of Springfield and the Cooley Dickinson Hospital of Northampton.

Entering active duty in the Army in October, 1942, he spent three years at Camp Myles Standish, Taunton, Mass., where he served as Chief of Medical Service from February, 1943, until relieved from active duty in December, 1945, with the rank of Lieutenant Colonel.

Dr. Barrett was a member of the Springfield Academy of Medicine and was its Treasurer in 1941–42. He belonged to the Osler Club, the Hampton County Medical Society, the Massachusetts Medical Society and the American Medical Association. He became a Fellow of the American College of Physicians in 1938. His interests and efforts, however, were not confined solely to his profession as he took an active and important part in the affairs of his community as evidenced by his membership in the Masons, the Kiwanis Club and the Reality Club of Springfield. His particular extra-professional interest was photography, and during numerous extensive vacation trips he developed this hobby to a high degree of proficiency.

Dr. Barrett was a valued member of his community and of his profession, and the College joins in extending sincerest sympathy to his wife, the former Sybil Jesseman whom he married in 1922, and to his two sons, Raymond L. Barrett, Jr., and Allen H. Barrett who survive him.

RICHARD P. STETSON, M.D., F.A.C.P.,
Governor for Massachusetts

DR. JOHN EIMAN

While enjoying a well-deserved vacation, Dr. John Eiman, F.A.C.P., died suddenly in Guadalajara, Mexico, on Dec. 3, 1954. With his passing, Pennsylvania loses an able physician and teacher and the American College of Physicians, a loyal Fellow.

Dr. Eiman was born near Riga, Latvia, in 1886, and came to the United States in 1907. He received his premedical education at Temple University and his medical education at the University of Pennsylvania School of Medicine from which he graduated in 1918. Very shortly thereafter, with all of the energy and enthusiasm that he applied to everything he undertook, he began working for the freedom of his native Latvia, which the successful end of World War I gave reason to hope for. This did not represent a new interest by any means; indeed, his youthful activity in the cause of Latvian freedom was the reason for his having to leave his native land in

1907. For his efforts in 1918 and later, and after its freedom had been gained, Latvia bestowed upon him the Order of Three Stars, Officer Grade.

Soon after the end of World War I, his active career as a pathologist began when in 1920, he was made Associate Pathologist and, in 1922, Assistant Professor of Pathology in the medical school of the University of Pennsylvania. In 1923 the long association with the Presbyterian Hospital of Philadelphia began. Some years later, he became Director of the Department of Pathology of the Abington Memorial Hospital in nearby Abington, Pa., a position which he filled with distinction until his death. He was a member of many medical organizations and made many contributions to the medical literature. He became a Fellow of the American College of Physicians in 1930.

Dr. Eiman was a person with a vivid personality. A man of courage, he was also a man of great sensitivity who could be deeply moved by great music as his friends well know. Perhaps his host of friends will remember best his great charm, his enjoyment of life, his love of people, and the tremendous enthusiasm which he gave to everything he undertook. Those who enjoyed his friendship will truly miss him.

THOMAS M. MCMILLAN, M.D., F.A.C.P.,
Governor for Eastern Pennsylvania

DR. JOHN M. RICE

Dr. John Marcus Rice, F.A.C.P., who was born May 31, 1908, in Watertown, N. Y., died Dec. 1, 1954, in his native city after a brief illness as the result of a subarachnoid hemorrhage.

Dr. Rice was graduated from Colgate University with an A.B. degree in 1929, and received his M.D. degree from Columbia University College of Physicians and Surgeons in 1933. He served as an intern at the Brooklyn Hospital for two years before entering the practice of medicine in Watertown in 1935, where he was Attending Physician at the House of the Good Samaritan and the Mercy Hospital from that time until his death.

Dr. Rice served in World War II and was attached to the 74th and 79th General Hospitals and was Chief of the Medical Service of the 74th General Hospital. He served from 1942 to December, 1945, and was discharged as a Major, (MC), AUS, having served in France, Northern Ireland, and England.

Dr. Rice was a member of the Jefferson County Medical Society, New York State Medical Society, Fellow of the American College of Physicians since 1948, Diplomate of the American Board of Internal Medicine, and a member of the American Medical Association.

Dr. Rice was a very capable internist and his opinion was respected by his colleagues and patients. The medical profession and the citizens of Watertown and Northern New York have suffered a distinct loss in the death of Dr. Rice.

EDWARD C. REIFENSTEIN, SR., M.D., F.A.C.P.,
Governor for Western New York

DR. HAROLD E. RYKERT

Dr. Harold Edmund Rykert, a Fellow of the American College of Physicians since 1949, died in Toronto on Nov. 15, 1954, following an operation to fuse a portion of the spine.

Dr. Rykert was born in Dundas, Ont., on July 28, 1904, the son and grandson of physicians. He was a person of unusual energy and vigor that were directed by an intellectual appreciation of his problems and a keen interest in everything that he did. This was well demonstrated as a student when, in addition to academic activity, he played well on the University of Toronto intercollegiate football team. It was

continued through several years of graduate training in Toronto and England when he won a reputation for industry, dependability and competence. On his return to Toronto, he threw his whole person into the study and teaching of heart disease and, in association with Dr. John Hepburn, recognized the electrocardiographic changes associated with left ventricular strain. His interest was never limited to the field of cardiology. He was an excellent physician, competent in all aspects of the care of his patients and in teaching students the basic principles of medicine and its practice. Throughout his life he maintained a great interest in the out-of-doors and in particular in his island in Lake Timagami, two hundred and fifty miles north of Toronto.

Dr. Rykert was graduated in medicine from the University of Toronto in 1928, and was appointed to the staff of the Faculty of Medicine and the Toronto General Hospital in 1933. He advanced through various stages to the rank of Associate Professor of Medicine and Senior Physician to the Toronto General Hospital. His academic activity was interrupted in 1939 when he went overseas with No. 15 Canadian General Hospital. About the time of his return, he began to be troubled with severe symptoms of disc disease which recurred again and again, being relieved temporarily by two operations. He continued in useful activity, little daunted and little influenced by two attacks of cardiac infarction. He undertook with vigor a long-term study of problems of hypertension and atherosclerosis, using the facilities of the Toronto General Hospital and of Sunnybrook Veterans' Hospital, where he was Senior Consultant in Cardiology. He demonstrated remarkable ability to stimulate young men in the furtherance of this work and he continued in persistent constructive activity in spite of excruciating nerve root pain, the severity of which was hidden from all but a few of his friends. He gained transient relief from this pain from a third operation at which large amounts of disc material were removed and following which the fusion was done.

Dr. Rykert, M.R.C.P. (Lond.) and F.R.C.P. (C), was a Fellow of the Academy of Medicine of Toronto, a member of the Ontario and Canadian Medical Associations and a former member of the Council of the American Heart Association.

RAY F. FARQUHARSON, M.D., F.A.C.P.,
Governor for Ontario

DR. HENRY F. SMYTH

Dr. Henry Field Smyth, Sr., a Fellow of the American College of Physicians since 1930, died in Pocasset, Mass., on Oct. 15, 1954, of arteriosclerosis with uremia.

Dr. Smyth was born in Germantown, Philadelphia, Nov. 1, 1875. He attended the University of Pennsylvania, receiving his medical degree in 1897, and his Doctorate in Public Health in 1912. Since 1912 he had been associated with the University of Pennsylvania School of Medicine, and in 1921, after serving as Assistant Professor of Bacteriology, was named Assistant Professor of Industrial Hygiene; this position he held until 1941. In 1942 he retired as Emeritus Professor of Industrial Hygiene. During World War I, he was on active duty with the U. S. Public Health Service Reserve as Assistant Surgeon. Throughout his career he was identified with investigations and activities in the field of industrial toxicology and established a laboratory bearing his name in Philadelphia. He contributed many articles to the literature concerning anthrax and dust hazards in industry and was the author of the book *Industrial Microbiology.*

After his retirement he lived in the village of Pocasset, where he and Mrs. Smyth, the former Clara Ellis, lived until his death. Up to about three years ago he did some consulting work; and during the early years of his retirement, he joined and took an active part in the Barnstable District Medical Society. Although his health had been failing over the past three years, he was still able to carry on some of his microscopic work and take an active interest in carrying out interpretations of

previously performed investigations until the spring of 1954, when an acute episode of cardiac failure occurred.

During his life he was a member of the American Public Health Association and served as a member of its Governing Council between 1923 and 1928. He was a member of the Health Commission of the Philadelphia Chamber of Commerce and between 1920 and 1924 served as Special Scientific Investigator, Pennsylvania Department of Labor and Industry. He also was a member of the Philadelphia Pathological Society, College of Physicians of Philadelphia and the American Medical Association. Consonant with his interests in industrial microbiology, he was active in the affairs of the Association of American Bacteriologists, American Association of Industrial Physicians and Surgeons, the Advisory Health Council of the National Safety Council and the American Association for the Advancement of Science. He was a member of the Phi Alpha Sigma and Sigma Xi fraternities.

Dr. Smyth lived a full professional life, contributing much both by his own investigations and the application of his contributions to the field of industrial hygiene. In his years of retirement he was in the happy position of being able to carry on activities in his chosen field and at the same time enjoy the relaxing pleasures of the quietude of a Cape Cod village. It can truly be said that his life was a full one and that through his activities he contributed much in the field of his choosing.

Richard P. Stetson, M.D., F.A.C.P.,
Governor for Massachusetts

DR. WALTER J. WILSON, SR.

Walter John Wilson, Sr., M.D., F.A.C.P., who died July 18, 1954, was born in Detroit, Feb. 6, 1876. He attended the Detroit College of Medicine and Surgery, where he obtained his M.D. degree in 1897, and received his Ph.C. at Wayne University College of Medicine. He was an Instructor in Pharmacy from 1902–14 and Assistant Professor of Therapeutics from 1914–29, later becoming an Associate Professor and finally Professor in 1935–48. From that time on, Dr. Wilson was Emeritus Professor of Clinical Medicine at Wayne University College of Medicine. During that period he was also Professor of Materia Medica at Detroit College of Pharmacy from 1920–49.

Dr. Wilson was a member of the staff of St. Mary's Hospital as Cardiologist beginning in 1912. He was Chief of Staff of that institution in 1940 and Executive Head of the Medical Department and Consultant in Medicine as well. He was Attending Cardiologist at the Veterans Administration Hospital from 1918–38. He was author of more than twenty articles on therapeutics and heart disease.

Dr. Wilson was also founder and first President of the Detroit Medical Club in 1906. He was a Vice President and Trustee of the Wayne County Medical Society, a member of the Michigan State Medical Society, and a member of the House of Delegates of the American Medical Association from 1919–22. He was a member of the Advisory Council of the American Heart Association and was a Diplomate of the American Board of Internal Medicine. He had been a Fellow of the American College of Physicians since 1919.

For many years, as his hobby, he joined other physicians in Detroit and frequently played volley ball with them at the Central Y. M. C. A. He was likewise an enthusiastic golfer. Dr. Wilson led an extremely well-rounded life, and during the period of his time in Detroit, he was an Elder of the First Presbyterian Church and was active in its affairs. He was unusually well liked by his patients, his friends, and members of the medical profession. His students always had praise for his efforts to impart to them his knowledge of cardiology. He was a fine man and a physician who followed the ideals set forth by the Great Physician.

H. Marvin Pollard, M.D., F.A.C.P.,
Governor for Michigan